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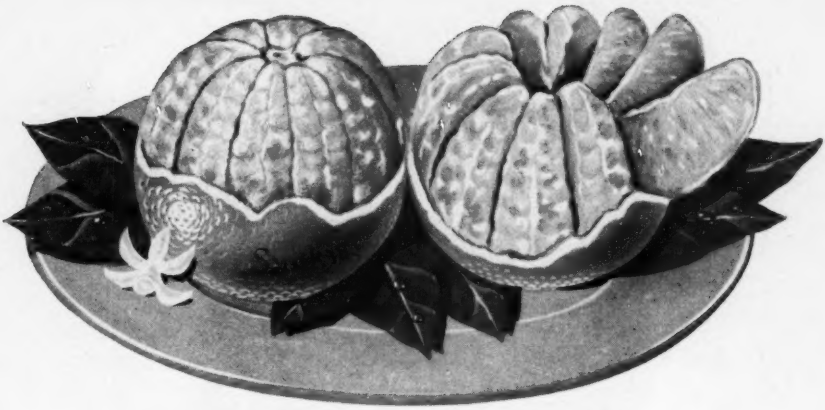

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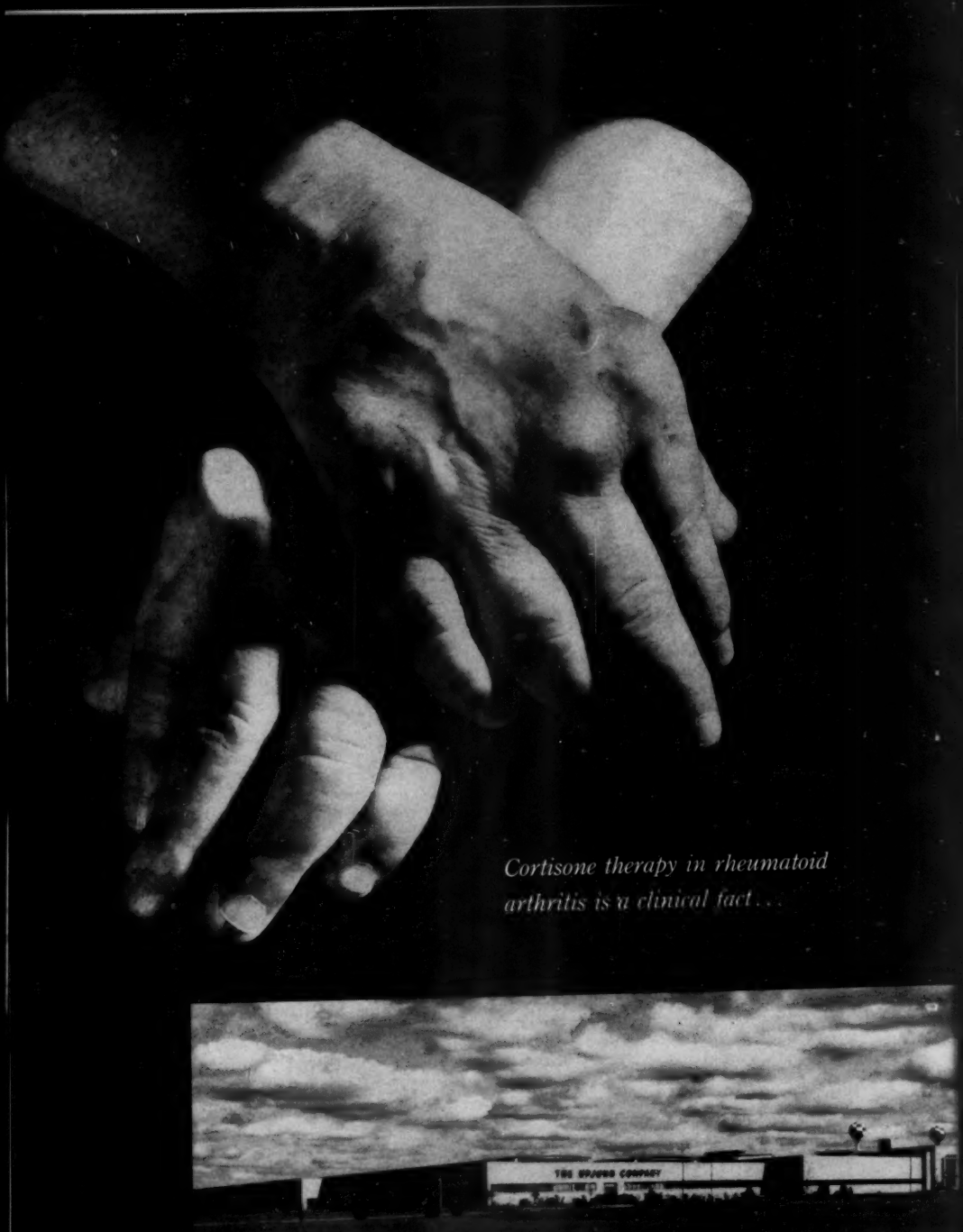

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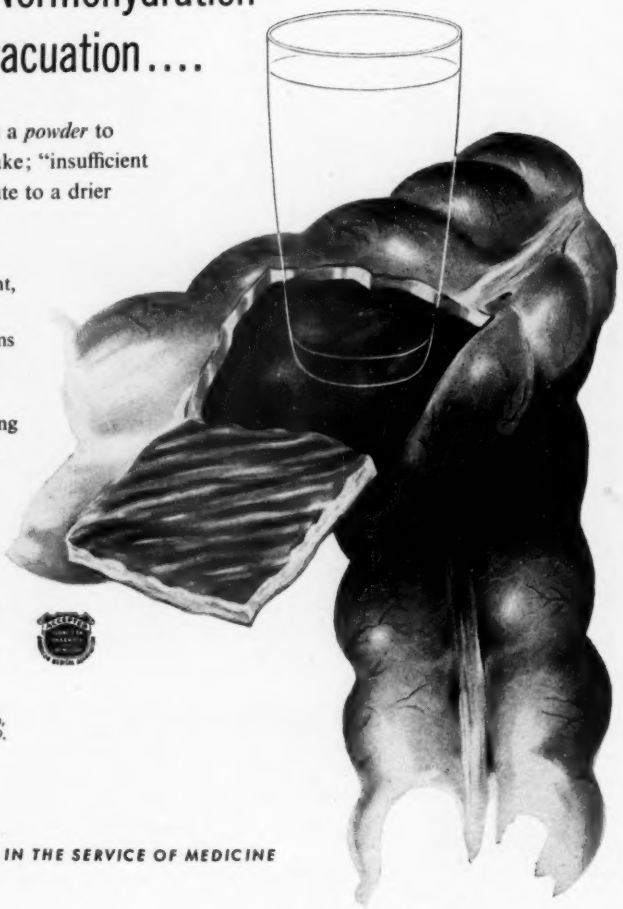

*Brown, P. W.: Symposium on Gastro-Intestinal Conditions: Constipation, M. Clin. North America 33:957 (July) 1949.

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A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 90 JULY 1952 NUMBER 1

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Editorials

LIGATION OF HEPATIC AND SPLENIC ARTERIES

THE CONTROL and treatment of hemorrhage arising from ruptured esophageal or gastric varices is one of the most difficult problems confronting the internist and surgeon. These varices in human beings usually are associated with portal hypertension. Efforts to control or prevent this type of hemorrhage have usually been directed toward the varicose veins themselves or toward the correction of the underlying problem of portal hypertension.

Esophageal bleeding has been arrested by methods such as insertion of suitable types of tubes with balloons, injection of the veins with sclerosing agents, excision of varices on the outside of the esophagus, excision of the lower third of the esophagus and the cardiac end of the stomach, and even excision of the entire stomach with an anastomosis between the esophagus and the jejunum. Other methods have been used in an attempt to decrease portal hypertension and thus decrease the vulnerability of the veins to rupture. Omentopexy was one of the earliest surgical attempts to produce a shunt of blood away from the portal stream. Splenectomy was likewise a procedure aimed to decrease the flow of blood to the liver. More recently, portacaval and splenorenal shunts have been devised which produce a bypass between portal and systemic circulation.

Of all the methods mentioned for the relief of portal hypertension, perhaps to date the most successful results have been obtained by either portacaval or splenorenal anastomosis. This type of operation is indicated almost exclusively for patients who have had hemorrhage resulting from portal hypertension and varices. It is not indicated for patients with cirrhosis whose main problem is poor liver function and associated ascites. It is reported that after successful portacaval anastomosis the portal pressure often is reduced to nearly normal, an enlarged spleen will shrink, and esophageal varices regularly become smaller or disappear entirely. This surgical procedure has been accomplished in a series of 111 cases by Blakemore,[1] with an over-all operative mortality rate of 16.2%. Of the 111 patients 79 had cirrhosis of the liver, and the operative mortality rate of this group was 20.2%.

Recently, a procedure has been developed for treatment of portal hypertension owing to cirrhosis of the liver. On the basis of animal studies [2] the hepatic and splenic arteries of selected patients with severe decompensated cirrhosis have been ligated. After this surgical procedure there has been noted clinical improvement.

1. Blakemore, A. H.: Portacaval Shunt for Portal Hypertension: Follow-Up Results in Cases of Cirrhosis of the Liver, J. A. M. A. **145**:1335-1339 (April 28) 1951.

2. Berman, J. K.; Koenig, H., and Saint, W. K.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension; Preliminary Report, Quart. Bull. Indiana Univ. M. Center **12**:99-102 (Oct.) 1950.

To understand better some of the reasoning behind such drastic surgical measures, a brief sketch of the problem is essential.

It is estimated that an average of about 1,500 cc. of blood goes through the liver of the human being each minute. The portal vein of a normal person carries about 75% of the total blood supply to the liver under a pressure of about 8 to 12 mm. of mercury. Approximately a third of this portal blood comes from the spleen. The hepatic artery carries the remaining 25% of the blood to the liver under a pressure of about 120 mm. of mercury.

Herrick,[3] in 1907, injected normal and cirrhotic livers with saline solution shortly after death and found in the normal liver that with an increase in arterial pressure the portal pressure changed very little. In the cirrhotic liver, however, as arterial pressure was increased the portal pressure was decidedly elevated. He concluded that there was more open communication between the portal and the arterial currents in the cirrhotic liver than in the normal liver, and that this communication was an important factor in an explanation of increased portal pressure in portal cirrhosis. Dock,[4] in 1942, confirmed the phenomenon noted by Herrick but found that it was not true in all cases of cirrhosis. He suggested for the first time the possible value of tying off the hepatic artery for the treatment of decompensated portal cirrhosis.

Recently, Berman and his associates [5] published a preliminary report in which they noted that on tying the hepatic artery in a dog close to the celiac axis a decrease occurred in portal pressure of 10 to 15 mm. of water in 20 minutes. After this, when the splenic artery was ligated close to the celiac axis, there was a gradual decrease in the portal pressure which equaled 70 to 80 mm. of water within half an hour. The two procedures reduced the portal pressure in this animal from 70 to 195 mm. of water to 70 to 80 mm. of water; no mention is made of the duration of this effect. Simultaneous measurement of blood pressure in the femoral artery did not show any decrease. A side-to-side portacaval anastomosis before ligation of the hepatic and splenic arteries did not change the results. These authors expressed the opinion that the pressure within the hepatic artery is probably one of the factors responsible for the increase in portal venous pressure. In discussion on this paper, Grindlay raised the question whether ligation of the hepatic artery is attended by an increased rate of portal flow, and, if so, for how long; he also questioned whether this ligation would have the same effect on the cirrhotic as on the normal liver. He pointed out that perhaps the great displacement and disarrangement of the branches of the portal vein in the liver might be the really significant impediment to portal flow, and that the factor of arterial inflow is insignificant by comparison.

Obviously ligation of the hepatic artery in certain positions does not deprive the liver entirely of arterial blood. It is well known that the liver will not survive if the branches of the hepatic artery are ligated as they enter the liver. It is true that

3. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93-104, 1907.

4. Dock, W.: The Role of Increased Hepatic Arterial Flow in the Portal Hypertension of Cirrhosis, Tr. A. Am. Physicians **57**:302-305 (May) 1942.

5. Berman, J. K.; Koenig, H., and Muller, L. P.: Ligation of Hepatic and Splenic Arteries in Treatment of Portal Hypertension: Ligation in Atrophic Cirrhosis of the Liver, A. M. A. Arch. Surg. **63**:379-389 (Sept.) 1951.

the use of penicillin may keep dogs whose hepatic arteries are so ligated alive for days or weeks, yet they die of massive hepatic necrosis unless the liver receives a new supply of arterial blood by way of collateral arteries.

Naturally such experimental studies were soon applied to human beings. Berman and his associates [5] mentioned that 10 patients having advanced cirrhosis of the liver, ascites, and esophageal varices underwent ligation of the hepatic and splenic arteries with favorable results, although the time since operation was too short to draw any conclusion. In November 1951, Berman and associates [6] reported a rather dramatic case of advanced decompensated portal cirrhosis in which the patient responded very favorably to ligation of the hepatic and splenic arteries. After six months this patient had had only slight recurrence of ascites, bleeding from esophageal varices had not occurred, and his strength, appetite, and general condition showed remarkable improvement.

Reinhoff [7] reported on six patients with alcoholic cirrhosis who had survived ligation of the common hepatic artery distal to the departure of the gastroduodenal artery in conjunction with ligation of the splenic artery. He noted clinically that manifestations of portal hypertension, such as bleeding from varices or ascites, have been helped considerably by this procedure. He stated that because the procedure is simple it might be preferable to some other methods of treatment for portal hypertension. There seems to be considerable disagreement on the point of its simplicity, however, since some excellent surgeons find the procedure very difficult.

The wide interest shown in hepatic circulation during the past few years gives hope that more facts will soon be available concerning this dynamic organ. Obviously, the value of ligation of the hepatic and splenic arteries for patients with cirrhosis, ascites, and esophageal hemorrhage is not now known. It does seem illogical, however, to deprive an already badly damaged organ of a good share of its blood supply. The possibility of further impairment of liver function must be expected in exchange for whatever benefit might be derived from relief of portal hypertension. It is important, nevertheless, that well-controlled clinical research continue in this field.

HUGH R. BUTT, M.D.

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6. Berman, J. K.; Muller, L. P.; Fisch, C., and Martz, W.: Ligation of the Hepatic and Splenic Arteries in a Patient with Atrophic Cirrhosis of the Liver, A. M. A. Arch. Surg. **63**:623-628 (Nov.) 1951.

7. Reinhoff, W. F., Jr.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension with a Report of 6 Cases: Preliminary Report, Bull. Johns Hopkins Hosp. **88**:368-375 (April) 1951.

CEREBRAL METABOLIC DISTURBANCE AND DELIRIUM IN PERNICIOUS ANEMIA

Clinical and Electroencephalographic Studies

DONALD C. SAMSON, M.D.
SYRACUSE, N. Y.
SCOTT N. SWISHER, M.D.
RICHARD M. CHRISTIAN, M.D.
AND
GEORGE L. ENGEL, M.D.
ROCHESTER, N. Y.

IT IS THE purpose of this paper to discuss the disturbance in cerebral function which occurs in pernicious anemia patients. This aspect of the disease process, while noted since the earliest descriptions of the disease, has remained poorly understood because of the lack of tools for proper study of such cerebral processes.

HISTORICAL REVIEW

In his classical description of pernicious anemia in 1849, Addison [1] may have recognized disturbance in cerebral function in the disease process, for he wrote as follows:

> Its approach is first indicated by a certain amount of languor and restlessness, to which presently succeed a manifest paleness of countenance, loss of muscular strength, general relaxation or feebleness of the whole frame, and indisposition to, or incapacity for, bodily or mental exertion.

Lichtheim [2] in 1887 first called attention to neurodegenerative changes in pernicious anemia and ascribed them to some blood-circulating toxin. In a poorly received paper, Langdon [3] in 1905 reported the first cases of neurological and psychological symptoms preceding the onset of blood changes and suggested that they might have a common cause.

The neurological disorder (combined system disease) has been sufficiently well defined that physicians in general are now quite familiar with the occurrence and character of spinal cord involvement in pernicious anemia.[4] However, they are

---

Commonwealth Fund Fellow in Medicine and Psychiatry (Dr. Samson).

From the Departments of Medicine and Psychiatry, Strong Memorial Hospital and Rochester Municipal Hospital, University of Rochester School of Medicine and Dentistry.

1. Addison, T.: Anemia: Disease of the Suprarenal Capsules, London Med. Gaz. **43**:517-518, 1849.

2. Lichtheim, H.: Zur Kenntniss der perniciösen Anämie, München. med. Wchnschr. **34**:301, 1887.

3. Langdon, F. W.: Nervous and Mental Manifestations of Pre-Pernicious Anemia, J. A. M. A. **45**:1635-1638, 1905.

4. Billings, F.: The Changes in the Spinal Cord and Medulla in Pernicious Anemia, Boston M. & S. J. **147**:225-233, 257-263, 1902. Dana, C. L.: Subacute Combined Sclerosis of the Spinal Cord and Its Relation to Anemia and Toxemia, J. Nerv. & Ment. Dis. **26**:1-19, 1899.

less familiar with the psychological disturbances in this disease. Nearly all the early cases reports describe psychological disturbances, and from 1900 to 1930 numerous papers [5] appeared which were devoted solely to the mental aspects of the disease. These were largely clinical reports on isolated cases usually presenting an overtly psychotic picture, but no clear distinction was made between organic and psychological factors.

At present there are no accurate statistics available on the incidence of psychological disturbances in pernicious anemia. As Bethell [6] has pointed out, one of the difficulties in making a study of disturbances of mental status in pernicious anemia patients is the fact that these patients are from the older age group, among whom degenerative disorders of the central nervous system are commoner. Woltmann [5j] in 1919 reported that 80% of 150 consecutive pernicious anemia patients exhibited evidence of damage to the nervous system. Thirty-five per cent of these patients showed "abnormal mentality." In 1932 Young,[7] reporting on 515 cases, stated that 4.5% exhibited "psychotic trends," including "acute deliriums, depressions, paranoid states, and memory and disposition changes." A recent paper [8] reports 25% of pernicious anemia patients as having "mental changes."

We believe that certain disturbances in behavior in pernicious anemia patients are secondary to disturbances in cerebral metabolism and that these are much commoner than has been recognized. Such behavioral alterations secondary to metabolic

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Hunter, W.: Pernicious Anaemia: Its Pathology, Septic Origin, Symptoms, Diagnosis, and Treatment, London, C. Griffin & Co., 1901. Putnam, J. J.: A Group of Cases of System Sclerosis of the Spinal Cord Associated with Diffuse Collateral Degeneration Occurring in Enfeebled Persons Past Middle Life and Especially in Women, J. Nerv. & Ment. Dis. **18**:69-110, 1891. Russell, J. D. R.; Batten, F. E., and Collier, J.: Subacute Combined Degeneration of the Spinal Cord, Brain **23**:39-110, 1900.

5. (*a*) Barrett, A. M.: Mental Disorders and Cerebral Lesions Associated with Pernicious Anemia, Am. J. Insanity **69**:1063-1078, 1913. (*b*) Hunter, W.: The Nervous and Mental Disorders of Severe Anaemias in Relation to Their Infective Lesions and Blood Changes, Proc. Roy. Soc. Med. **16**:(Sect. Med.) 1-4, 1922-1923. (*c*) Lurie, L. A.: Pernicious Anemia with Mental Symptoms: Observations on the Varying Extent and Probable Duration of Central Nervous System Lesions in 4 Necropsied Cases, Arch. Neurol. & Psychiat. **2**:67-109, 1919. (*d*) McAlpine, D.: Nervous and Mental Aspects of Pernicious Anemia, Lancet **2**:643-647, 1929. (*e*) McCrae, T.: Nervous Manifestations of Pernicious Anemia, Bull. Johns Hopkins Hosp. **13**:61-62, 1902. (*f*) Pickett, W.: Mental Symptoms Associated with Pernicious Anemia, Am. J. M. Sc. **127**:1032-1036, 1904. (*g*) Rogers, A. W.: Disturbances of the Central Nervous System Accompanying Pernicious Anemia: Report of 2 Cases, J. Nerv. & Ment. Dis. **42**:693-699, 1915. (*h*) Warburg, E. J., and Jørgenson, S.: Psychoses and Neurastheniæ Associated with Achylia Gastrica and Megalocytosis, and the Relation Between This Syndrome and Pernicious Anæmia: Psychoses, Acta med. scandinav. **69**:537-592, 1928. (*i*) Woltmann, H. W.: Brain Changes Associated with Pernicious Anemia, Arch. Int. Med. **21**:791-843, 1918; (*j*) The Nervous Symptoms in Pernicious Anemia: An Analysis of 150 Cases, Am. J. M. Sc. **157**:400-409, 1919; (*k*) The Mental Changes Associated with Pernicious Anemia, Am. J. Psychiat. **3**:435-449, 1924.

6. Bethell, F. H., and Sturgis, C. C.: The Relation of Therapy in Pernicious Anemia to Changes in the Nervous System: Early and Late Results in a Series of Cases Observed for Periods of Not Less Than 10 Years, and Early Results of Treatment with Folic Acid, Blood **3**:57-67, 1948.

7. Young, R. H.: Neurologic Features of Pernicious Anemia, J. A. M. A. **99**:612-614, 1932.

8. Slepian, A., and Vaughan, S. L.: Nervous System Manifestations in Pernicious Anemia, New York J. Med. **51**:1524-1526, 1951.

changes constitute a syndrome of delirium as we have defined it in earlier publications.[9] By the application of appropriate techniques, such abnormalities are readily demonstrable in many patients with pernicious anemia.

TECHNIQUES FOR STUDY OF DELIRIUM

The first technique for study of delirium stems from the delineation of the concept of delirium [9] in which the total behavior of the delirious patient is interpreted in terms of a release from higher cerebral control, due to damage to the brain itself, the organ of the ego. The basic and consistent psychological manifestation of this is a disturbance in the level of consciousness, which in turn is dependent upon the underlying physical disorders. This may be manifested by drowsiness with incomplete awakening, decreased ability to maintain attention, decreased ability to perceive and interpret external stimuli, disorientation, reduced ability to utilize abstract concepts with return to more concrete concept patterns, and, when extreme, stupor or coma. Associated with the disturbance in level of awareness, which typically fluctuates, may be various release phenomena, including anxiety, panic, regressed infantile behavior, incontinence, and primitive motor behavior, such as picking, grasping, and groping. The more individual behavioral aspects of the delirium, the content of thought, the nature of the psychological adaptive devices utilized by the patient, and the presence and content of hallucinations, frightening dreams, and fantasies are more dependent upon the previous life experience and psychological development of the patient than upon the nature of the underlying physical process. Thus, delirium, as it relates to cerebral metabolic disturbance, can be clinically diagnosed by attention to the manifestations related to the reduction in the level of consciousness, particularly by specific testing of attention, memory, and capacity for abstract thinking. The most valuable single test has been the serial subtraction of numbers, such as 3 from 100.

The second tool for study of delirium is the electroencephalograph. Electroencephalographic changes are found in patients with disturbances in consciousness consequent to physical disease, drug administration, hypoxia, hypoglycemia, etc.[10] These changes are reversible to the extent to which the clinical delirium is reversible. In studies of delirium occurring spontaneously in the course of various diseases [10] and induced experimentally by anoxia,[11] hypoglycemia,[11] and the administration of alcohol [12] and other toxic materials,[13] the electroencephalograph provides a sensitive indicator of changes in the physiologic status of the cerebral cortex in such circumstances. With the use of a quantitative method of analysis of frequency distri-

9. Romano, J., and Engel, G. L.: Physiologic and Psychologic Considerations of Delirium, M. Clin. North America **28**:629-638, 1944.

10. Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, Arch. Neurol. & Psychiat. **51**:356-377, 1944.

11. Engel, G. L.; Webb, J. P., and Ferris, E. B.: Quantitative Electroencephalographic Studies of Anoxia in Humans: Comparison with Acute Alcoholic Intoxication and Hypoglycemia, J. Clin. Invest. **24**:691-697, 1945.

12. Engel, G. L., and Rosenbaum, M.: Delirium: III. The Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, Arch. Neurol. & Psychiat. **53**:44-50, 1945.

13. Engel, G. L.; Romano, J., and Goldman, L.: Delirium: IV. Quantitative Electroencephalographic Study of a Case of Acute Arsenical Encephalopathy, Arch. Neurol. & Psychiat. **56**:659-664, 1946.

bution,[14] it has proved possible to correlate the level of consciousness with changes in frequency distribution. In general, reduction in the level of awareness is associated with a shift toward slower frequency ranges.

The third technique for study of changes in cerebral metabolism is the nitrous oxide method for determining cerebral blood flow, as devised by Kety and Schmidt [15] and modified by Scheinberg and Stead.[16]

The first published electroencephalographic studies in pernicious anemia were reported in 1944 by Romano and Engel.[10] In this report were included data on two patients with pernicious anemia, both of whom showed abnormal electroencephalograms. With treatment, one patient's mental status and electroencephalogram changed from marked abnormality to normal limits, and the other patient showed little or no change.

Recently Scheinberg [17] has reported his observations on 16 patients with pernicious anemia studied with the nitrous oxide technique for determining cerebral blood flow and oxygen consumption. In patients whose hemoglobin content was below 7 gm. per 100 cc., cerebral blood flow was increased and cerebral vascular resistance decreased. In patients with no anemia or with hemoglobin levels above 7 gm., cerebral blood flow was decreased and vascular resistance increased. He found no correlation between the anemia and the reduction in cerebral metabolism but did find a good correlation among "mental status defects," severity of neurological involvement, and the cerebral oxygen consumption. Electroencephalograms were done on 11 patients, and 8 were found to have "abnormal tracings." These observations are valuable because they objectively demonstrate, on one hand, the effects of anemia on cerebral circulation and, on the other hand, the effects of the deficiency state on cerebral metabolism. However, mental status was not evaluated from the point of view of delirium, and the electroencephalograms were not quantitatively analyzed or serially followed.

We feel that the present study is indicated in order to determine the incidence of disturbed cerebral metabolism and delirium in an unselected group of pernicious anemia patients and to investigate the relation of these changes to the more familiar hematologic abnormality.

METHODS AND MATERIAL

Since July, 1949, we have studied 14 consecutive patients with pernicious anemia. The diagnosis of pernicious anemia was based upon characteristic history and results of physical examination, macrocytic anemia, achlorhydria, and bone marrow showing megaloblastic erythropoiesis. Mental status examinations and electroencephalograms were obtained on admission, after

14. Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on the Effects of Physiological Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on Normal Electroencephalogram, Arch. Neurol. & Psychiat. **51**:134-146, 1944.

15. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Invest. **27**:476-483, 1948.

16. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Normal Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163-1171, 1949.

17. Scheinberg, P.: Cerebral Blood Flow and Metabolism in Pernicious Anemia, Blood **6**:213-227, 1951.

two to four days of bed rest, and serially after the beginning of specific treatment. Careful attention was given to other possible causes for delirium, including drug or alcohol ingestion, nutritional deficiencies, recent head injuries, aging process, etc. Blood urea nitrogen, sugar, and bromide levels were determined, and in two patients a lumbar puncture was performed. In none of these 14 patients could we find any factors, other than those involved in pernicious anemia, to account for the delirium. The clinical examination for delirium included the traditional mental status examination, with particular attention directed toward the level of awareness. This included observations on the patient's ability to attend to questioning and examination, the degree

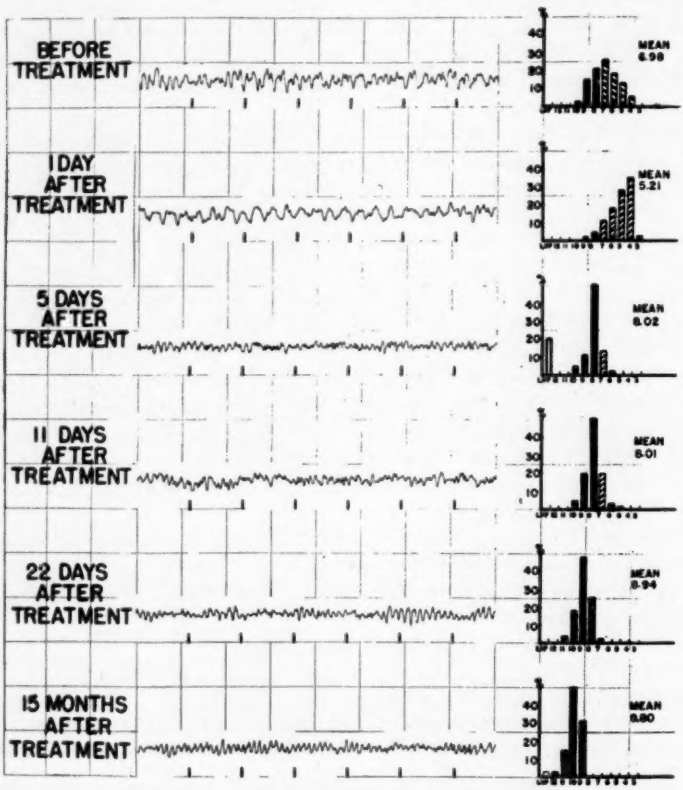

Fig. 1.—Patient E. S., a man aged 73. Serial electroencephalographic changes before and during treatment of pernicious anemia with vitamin B_{12}. Sample strips of electroencephalogram and spectra to the right illustrate progressive changes in electroencephalogram during course of treatment. Hematocrit percentages are shown by cross hatched columns. See text for more detailed description of clinical course.

to which this attention fluctuated, the speed and accuracy of responses, and the accuracy of orientation. The serial subtraction of 3 or 7 from 100 was a convenient method of testing those persons who had had at least a grammar-school education. One noted the time necessary to complete the test, the number of errors, the patient's reaction to the test or to the errors, and his increased effort, hesitation, or evasion. The manner of performance was of as much value as the arithmetical performance as an indicator of the level of awareness.

A six-channel Grass electroencephalograph, Model 3C, was used for these studies. Bipolar and monopolar tracings were obtained from the eight traditional electrode placements. A quantitative estimate of frequency distribution was obtained by the methods described in detail elsewhere.[18] Briefly, it consists of counting the number of waves for each second over a 300-second interval. From this a spectrum is constructed of the percentage of second intervals containing 1 to 14 waves, respectively (the range of countable frequencies in this series) as well as the percentage of seconds with uncountable waves (see Fig. 1). From this could also be calculated a mean frequency for the entire record. The distribution of frequencies and the mean frequency were then correlated with the changes in mental status and the hematologic status.

RESULTS

Thirteen of the 14 patients were delirious by clinical criteria. The degree of delirium varied widely. Six patients showed such markedly reduced level of consciousness and such disturbed behavior that the delirium was manifest without need for specific examination. Seven patients had a significant reduction in the level of consciousness but were able to control the external manifestations in such a way that the diagnosis might have been missed had not specific tests been done. They were able to give their history, knew where they were, spoke of being tired, and occasionally were unable to recall dates of previous illnesses. But when specifically tested, there was a fluctuation in level of awareness and inability to attend or to do abstract thinking for any length of time. It may well be that failure to recognize the latter group of patients as being delirious in previous studies on pernicious anemia is responsible for some of the varying percentages of mental abnormalities that have been reported.

Illustrative case histories of these two extremes are as follows:

E. S. (299203) was a 73-year-old retired salesman of English descent. Admitted in July, 1949, he complained of dizzy spells, lightheadedness, dyspnea, and palpitation on exertion of six months' duration. There had been weakness and staggering, but no numbness, tingling, or anesthesia. There had been loss of appetite and a weight loss of 8 lb. (3.6 kg.), but no other gastrointestinal symptoms.

On examination he was well oriented but spoke slowly and hesitatingly. He was pleasant and cooperative and effectively hid his reduced level of awareness with a smiling affability. However, when requested to do serial subtraction of numbers, he was very slow and made frequent errors. On repeated questioning, it was obvious that his memory was impaired, as details of his history were not consistent from one interview to the next. There was a yellow tint to the skin. The tongue was large, pale, and smooth. The chest showed evidence of emphysema. A Grade I systolic murmur was present at the apex. No abdominal organs or masses were palpable. There were no neurological signs of subacute combined cord degeneration. The red blood cell count was 1,450,000 per cubic millimeter; the hemoglobin concentration was 5.8 gm. per 100 cc.; the white blood cell count was 2,550 per cubic millimeter; the blood smear showed typical findings of pernicious anemia. The urine was normal. There was achlorhydria after histamine administration. The electroencephalogram showed slowing characteristic of delirium, with a mean frequency of 6.98 waves per second and a range of 4 to 10 per second. He became more delirious, and the electroencephalogram became slower during the first five to six days in the hospital but then showed progressive improvement beginning on the third or fourth day of treatment. Fifteen months later the mean frequency was 9.80 waves per second, with a range of 9 to 12 per second (Fig. 1).

This patient demonstrated a type of delirium which often goes undetected because of the absence of flagrant behavioral disturbances but which may be nonetheless serious as far as permanent damage to nerve cells is concerned.

18. Footnotes 11 to 14.

The next patient showed delirium with behavioral disturbances so manifest that no specific examinations were necessary to make the diagnosis.

E. M. (306819) was a 57-year-old housewife of Irish descent, who was admitted to the hospital in April, 1950. Two to three years before, the patient noted onset of ankle edema late in the day. Varicose veins were treated by injection one year before. During the six months prior to admission, she had noted numbness and tingling of legs and arms, increasing weakness, tiredness, dyspnea on exertion, decrease in appetite, and "soreness of the stomach."

On examination it was readily noted that the patient was tired. She was unable to maintain attention consistently. She appeared confused, bewildered, and unable to comprehend the meaning of the examination. As the history was elicited, she was inattentive and unable to make relevant associations and tended to wander off onto unrelated topics. She was oriented as to time, place, and person but became tense and mildly agitated when pressed for any details. She bluntly refused to attempt some tests and misinterpreted a proverb. Serial subtraction was done correctly but slowly and with hesitation on the first occasion and with numerous errors two days later. There was obvious fluctuation in her level of awareness from hour to hour. The skin had a yellow tint and the tongue was smooth. The liver was palpable 2 cm. below the right costal margin. She had ataxia, decreased position sense in both legs, and absent vibratory sensation at both ankles. The red blood cell count was 1,200,000 per cubic millimeter; the hemoglobin concentration was 5.5 gm. per 100 cc.; the white blood cell count was 3,400 per cubic millimeter. The smear was characteristic of pernicious anemia. The urine was normal. The gastric analysis with histamine revealed no free acid. The electroencephalogram showed a moderately high voltage record, with dominant frequency of 6 to 7 waves per second, some 4- to 5-per-second activity, and a mean frequency of 6.39 waves per second. There was marked improvement in level of awareness and electroencephalogram within six days of the peak of the reticulolyte response to vitamin B_{12}. Dominant frequency became 7 to 8 waves per second, with a mean frequency of 7.63 waves per second (Table).

As in our earlier studies of delirium, the electroencephalographic findings correlated well with the clinical findings. Eleven patients had abnormally slow records with considerable activity of 7 per second and slower. In general, the patients with the most marked slowing were those with the most marked reduction in consciousness. One patient who was delirious but who had a normal electroencephalogram showed a significant increase in frequency during treatment, the mean frequency changing from 8.76 to 10.56 per second. Another patient (F. W.) also had a normal record which became somewhat faster with treatment, but he was not followed long enough to establish the significance of the change. The one patient who was not delirious clinically had a normal record which did not change with treatment.

All 14 patients responded hematologically, some suboptimally, to treatment. Seven of the patients were being used for assay purposes, so that the activity and amount of anti-pernicious-anemia substance was not known at the time of the study. The suboptimal response in some was due to inadequate dosage. The delirium in one patient (L. M. [306816]) responded to transfusion alone, but there was a further improvement on vitamin B_{12} therapy. Ten of the 13 delirious patients had complete clearing of the delirium; 2 patients showed improvement but persistent evidence of organic brain disease, and 1 patient, aged 82, remained unchanged. One patient (H. P.) had paranoid behavior, along with significant reduction in the level of consciousness. On admission this patient was weak and tired. He talked slowly, rambled considerably, and was aware of memory impairment, to which he responded in both an angry and a tearful manner. He was oriented as to time, place, and person and exhibited no delusions or hallucinations. Serial subtraction of numbers

*Summary of Data on Fourteen Patients with Pernicious Anemia**

Patient; Hospital Number; Age; Sex	Red Blood Cell Count † and/or Hemoglobin Concentration		Mental Status		Electroencephalogram, Waves/Second				Neurological Signs	Comment ‡
					Before Treatment		After Treatment			
	Before Treatment	After Treatment (2-3 Wk.)	Before Treatment	After Treatment	Lowest Frequency	Mean Frequency	Lowest Frequency	Mean Frequency		
L. W. 323493 80; F	2.0 m./cu. mm.	3.3 m./cu. mm.	Delirium manifest	Clear	5	6.45	6	7.39	Present	Vitamin B_{12}, 1 γ I. M. per day
H. P. 59431 47; M	1.75 m./cu. mm.	3.4 m./cu. mm.	Delirium manifest	Clear	6	7.77	9	11.59	Present	Vitamin B_{12}, 15 γ I. M. daily for 1 wk., then 3 times weekly
J. R. 221733 79; M	4.3 gm./100 cc.	9.2 gm./100 cc.	Delirium manifest	Improved but still delirium	4	5.87	Unable to repeat	Unable to repeat	Present	Transfusion; vitamin B_{12}, 50 γ I. M. daily
E. M. 306819 57; F	5.5 gm./100 cc.	10.0 gm./100 cc.	Delirium manifest	Clear	4	6.39	6	7.63	Present	Vitamin B_{12}, 15 γ I. M. daily
H. O. 50575 75; F	4.7 gm./100 cc.	8.25 gm./100 cc.	Delirium manifest	Clear	6	7.46	6	8.37	Present	2 wk. before admission had "liver shot" of unknown unKage; hospital treatment; 1 cc. reticulogen® § twice weekly
J. W. 310419 56; M	1.8 m./cu. mm.	2.94 m./cu. mm.	Delirium on examination	Clear	7	8.76	8	10.56	Present	Postgastrectomy pernicious anemia; vitamin B_{12}, 30 γ I. M. every other day
W. M. 163769 44; M	1.35 m./cu. mm. 5.0 gm./100 cc.	3.49 m./cu. mm. 10.2 gm./100 cc.	Delirium on examination	Clear	6	7.52	Unable to repeat	Unable to repeat	Present	Liver extract, 1 unit per day for 5 days, 40 units per day thereafter
A. B. 303271 73; F	1.2 m./cu. mm.	1.8 m./cu. mm.	Delirium on examination	Clear	6	8.14	7	9.08	Present	Liver extract, 1 unit daily
G. S. 193730 82; M	2.0 m./cu. mm.	2.3 m./cu. mm.	Delirium on examination	No change	3	5.09	4	5.97	Present	Concentrated liver extract, 40 units every 3d day
L. M. 306816 62; F	0.68 m./cu. mm.	3.33 m./cu. mm.	Delirium on examination	Clear	4	6.30	8	9.38	Present	Blood transfusion, 1,000 cc., cleared delirium
J. K. 248786 64; M	1.3 m./cu. mm.	2.6 m./cu. mm.	Delirium on examination	Clear	7	8.24	7	8.29	Present	Oral use of liver fortified with stomach and vitamin B_{12}, 6 capsules daily (130 γ vitamin B_{12} daily)
F. W. 321587 75; M	2.54 m./cu. mm.	3.6 m./cu. mm.	Delirium on examination	Clear	8	8.84	8	9.23	Present	Liver extract, 1 unit per day
E. S. 299203 73; M	1.25 m./cu. mm.	3.39 m./cu. mm.	Delirium on examination	Improved but still delirium	4	6.98	7	8.94	None	Vitamin B_{12}, 0.9 γ daily
H. M. 316327 62; M	1.5 m./cu. mm.	2.8 m./cu. mm.	Clear	Clear	7	8.75	8	8.66	None	Vitamin B_{12}, 1.5 γ daily

* Under mental status we have listed delirium manifest and delirium on examination. As explained in body of paper, manifest delirium is that disturbed behavior which is readily observed without careful examination of the level of awareness. Delirium on examination is that cerebral disturbance which is found only on careful examination of the level of awareness by such tests as the serial subtraction of numbers. Delirium cleared in 6 of the 14 patients before any appreciable rise in the red blood cell count or hemoglobin concentration was detected.

† Millions is indicated by m.

‡ I. M. is intramuscularly.

§ Concentrated purified liver extract with added thiamine hydrochloride.

was poorly performed. His talk was filled with suspiciousness and derogatory comments toward relatives, friends, and physicians he had known. After treatment these paranoid trends persisted, in spite of return to normal of his memory and his ability to do serial subtraction of numbers. The electroencephalogram also returned to normal limits with the clearing of the delirium.

It was possible to follow the electroencephalogram serially with a quantitative frequency analysis in 11 patients. The clinical condition of three patients prevented us from getting sufficient electroencephalograms to follow their course, although the records were all analyzed. The correlation between electroencephalogram and clinical response was again good. Nine of the 11 patients followed serially showed significant improvement in the electroencephalogram during treatment, the record becoming completely normal in 6. One patient was not delirious and had a normal

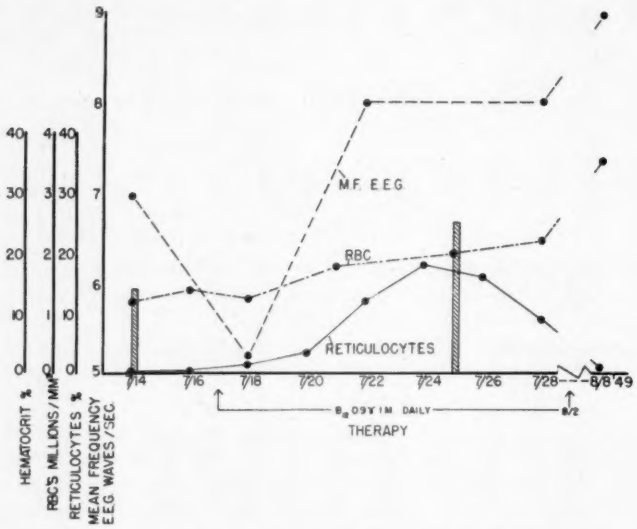

Fig. 2.—Patient E. S., a man aged 73. Graph illustrates relationship between electroencephalographic changes and blood changes, as indicated by mean frequency of electroencephalogram; brain waves became slower and patient became more delirious during first five or six days in hospital. During treatment with 0.9 γ of vitamin B_{12} intramuscularly, delirium improved and electroencephalogram accelerated about the same time that reticulocyte response began and before significant change in red blood cell count.

electroencephalogram which did not change; one patient showed no change in mental status or electroencephalogram.

Improvement in mental status and electroencephalogram preceded the maximum reticulocyte response by two days in one patient, occurred at about the same time in seven patients, and followed within six days in two others. We have reason to believe that because of the relatively short period of observation we did not see the maximum degree of improvement in all our patients, since the three patients on whom electroencephalograms were obtained 8, 13, and 15 months later all showed further improvement.

In Figure 2 we have graphically depicted the response of the reticulocytes, red blood cells, and electroencephalogram upon administration of 0.9γ of vitamin B_{12} daily. The patient was delirious on admission and became somewhat worse during the next four days. The first clinically noticeable improvement in delirium occurred five days after the first injection of vitamin B_{12}, at which time the electroencephalogram had changed considerably toward the normal and the reticulocyte count was rising. The electroencephalographic changes in the same patient are presented in Figure 1.

COMMENT

In this series of 14 consecutive patients with pernicious anemia, delirium was found to be present in 13 patients. The electroencephalograms in these 13 patients showed slowing in frequency of the waves such as has been shown to be characteristic of delirium of many different origins.[19]

Neurological evidence of some degree of spinal cord degeneration was found in 12 of the 14 patients. Thus, evidence of cerebral cortical involvement was as common as the better known spinal cord disease.

The results of carefully repeated studies of level of awareness before, during, and after the administration of vitamin B_{12} perhaps have bearing on the often-made observation that a sense of well-being comes on soon after potent therapeutic agents are given to patients with pernicious anemia. These observations seem to indicate that this sense of well-being might be related to the improvement which occurs in the disturbed cerebral metabolism and the consequent enhancement of integrative and perceptive faculties.

The fact that improvement in cerebral metabolism occurred in the majority of our patients after vitamin B_{12} therapy and that this improvement occurred before any significant rise in red blood cell count was noted would seem to indicate that the antianemia factor is in some way directly concerned with cerebral metabolic function and that such a disturbance is a highly consistent feature of the disease pernicious anemia. Of the 13 delirious patients, 10 recovered completely from their delirium, 2 improved but went on to show permanent organic brain damage, and 1 did not change. There is a need to study further the factors responsible for the failure of the delirium to clear in some patients. The duration of the delirium without treatment, the degree of anemia, malnutrition, and cerebral arteriosclerosis or age changes may be some of the factors affecting the reversibility of the disturbed cerebral metabolism. The electroencephalogram may prove a useful adjunct to the laboratory devices available to control the efficacy of specific therapies.

It should also be emphasized that the effect of the therapy was primarily on the level of awareness and on the behavioral disturbances consequent to the reduced awareness. There were no demonstrable effects on the more personal aspects of behavior. The underlying character structure and basic modes of behavior were not influenced. This was clearly evident in the patient with paranoid trends who showed a decided improvement in his level of awareness but no change in his paranoid behavior. There is no reason to anticipate from our studies that vitamin B_{12} or related antianemia factors will have any usefulness in other psychiatric disorders or even in delirium in patients other than those with pernicious anemia.

19. Footnotes 9 to 13.

SUMMARY

In a series of 14 consecutive pernicious anemia patients admitted to a general hospital in hematologic relapse, 13 had clinically demonstrable reduction in the level of consciousness, justifying the diagnosis of delirium. This was presumed to be consequent to a disturbance in cerebral metabolism and was accompanied with more or less reversible electroencephalographic changes.

By the use of serial mental status examinations and electroencephalograms before, during, and after treatment, it was demonstrated that the delirium and electroencephalogram began to improve about the time the reticulocyte response began, suggesting that the cerebral defect is a primary metabolic one and not secondary to the anemia.

Delirium was as common a finding in pernicious anemia as was combined system disease.

With active treatment the defect in cerebral metabolism is reversible in most patients.

The electroencephalogram is a clinically useful and available tool for studying cerebral metabolic changes and following the course of therapy in pernicious anemia.

University Hospital (Dr. Samson).

THE DYING HUMAN HEART

Electrocardiographic Study of Forty-Three Cases, with Notes upon Resuscitative Attempts

CHARLES D. ENSELBERG, M.D.
NEW YORK

IT IS the purpose of this paper to describe the behavior of the human heart during death as reflected in the electrocardiogram and to discuss certain features of this behavior, particularly as they relate to resuscitative attempts. The ancients believed that the heart was the last organ to die. Galen, as cited by Harvey,[1] stated that the order of death in the heart itself was cessation first of the left ventricle, then of the left auricle, then of the right ventricle, and finally of the right auricle. Harvey [1] extended these observations and concluded that the auricles were the *"primum vivens, ultimum moriens"*—the first part to live (in the embryo), the last to die. In this connection he mentioned the occasional occurrence of ventricular contractions at a rate much slower than that of auricular contractions in dying animal hearts. Harvey also described an instance of resuscitation of a pigeon's heart after death by keeping his wetted finger in contact with the motionless heart for a short time, after which it was "recalled, as it were, from death to life."

Though it has been known or suspected for centuries that the heart may continue to beat after apparent death, there are few authentic cases in the literature. One such case was well described in 1858.[2] A criminal was executed by hanging, and when his body was lowered 25 minutes later he was pronounced dead by the physician in attendance. One and a half hours after the hanging, during the performance of an autopsy, slight pulsatory movements were noted in the right subclavian vein. At this time direct auscultation of the chest revealed a regularly occurring single heart sound at a rate of 80 per minute. Upon exposure of the heart, the right auricle was seen to be in "full and regular motion, contracting and dilating with beautiful distinctness and energy." These movements continued at gradually slower rates and with occasional standstills for another three hours. It was then found that upon mechanical stimulation the beats were resumed, especially when stimulation was applied to the region where the venae cavae enter the auricle. Finally, 5 hours 18 minutes after the hanging no further activity could be provoked.

It is possible that a similar incident may have been responsible for Vesalius' banishment from Spain in 1563 or 1564. There are no authentic documents, but

From the Medical Division of Montefiore Hospital, New York Polyclinic Medical School and Hospital, and Gouverneur Hospital.

1. Harvey, W.: Exercitatio anatomica de motu cordis et sanguinis in animalibus, Frankfort, 1628; translated by R. Willis, London, Sydenham Society, 1847.

2. Clark, H. G.: Execution of Magee: Post-Mortem Appearances, Ext. Rec. Boston Soc. M. Improvement **3**:241, 1858.

Summary of Cases *

Case No.	Age	Diagnosis	Terminal Rhythms †	Length of Preterminal Asystoles, Sec.	Resuscitative Measures	Comment
1	62	Myocardial infarction	N.R. (I.V.R.?)	.....	Plasma infusion	Sudden death during recording of ECG, 5 hr. after onset
2	60	Lobar pneumonia; toxic hepatitis; ASHD	S.T.; A.Fl.-Fib.; ventricular standstills	3, 3, 4, 9, 6, 8 (all ventricular standstills)	.....	Final deflections, A.Fl.
3	70	Myocardial infarction	V.T. (S.V.T. with BBB?); A.Fib.; ventricular standstills; V.Fib.	8, 9, 6, 11.5 (all ventricular standstills)	Epinephrine; nikethamide	Died 1½ hr. after onset
4	60	Myocardial infarction ‡; thyrotoxicosis	A.Fl.; A.T. or S.T.; V.P.S.; V.T.; V.Fib.	.....	.....	Sudden death at onset of V.Fib. 6 min. after acetyl strophanthidin (1.2 mg.)
5	45	Pulmonary infarction ‡ after cholecystectomy	N.R.; I.V.R.	.....	.....	ECG recording ended when patient pronounced dead, though final asystole not recorded
6	57	Myocardial infarction	I.V.R.	.....	.....	Sudden death a few minutes after chest pain and shock
7	63	Carcinomatosis of ribs, pleura, and lungs; primary site unknown	Incomplete A-V block up to 4:1; V.P.S.; complete A-V block; intermittent V.T.	.....	.....	Sudden death
8	32	Glomerulonephritis ‡; fibrinous pericarditis; uremia	V.Fib.?; V.T.; V.Fl.; V.Fib.; V.T.; I.V.R.; asystoles; V.Fib.	6, 8, 5, 9	Procaine amide hydrochloride; atropine	Serum K, 3.5 mEq./L., 2 days before death
9	72	Myocardial infarction	I.V.R.; asystoles; bigeminy; I.V.R.	20, 7, 30	.....	Died 1 hr. after onset
10	68	Myocardial infarction	R.S.R.; inverted P waves; S.V.T. with A-V block; ventricular standstills and S.T.; R.S.R.	9, 12, 4, 8, 15, 10, 12 (all ventricular)	Intra-arterial transfusion	Last ventricular deflections 15 min. after clinical death; final deflections auricular
11	42	RHD; bronchopneumonia	A.Fl.-Fib.; V.P.S.; asystoles; V.T.	3, 5, 4, 30	Epinephrine	Recording ended when patient pronounced dead, though final asystole not recorded
12	65	Bronchopneumonia; ASHD	S.T.; A.Fib.; V.T.; asystoles; I.V.R.	9, 12	.....	Ouabain (0.5 mg.) given for acute pulmonary edema 45 min. before death
13	80	Myocardial infarction	R.S.R.; V.P.S.; A.Fib.; I.V.R.; asystoles; V.T.; V.Fib.	26, 38	Plasma and blood transfusions	Died 20 hr. after onset; 1.2 gm. of quinidine in 16 hr.
14	76	Myocardial infarction	I.V.R.; asystoles	10	Plasma; epinephrine; ephedrine; nikethamide	Died 11 hr. after onset

15	65	ASHD; myocardial infarction?	S.T.; asystoles; incomplete A-V block; V.P.S.; S.B.; I.V.R.; bifocal V.P.S.	12, 4, 5	Intra-arterial transfusion	Died 14 hr. after onset
16	80	ASHD	N.T.; I.V.R.; S.V.T. with complete A-V block; disappearance of P waves; asystole; I.V.R.	14	Phenylephrine; epinephrine	Sudden death while apparently improving on heart failure regimen
17	28	Ulcerative colitis; hypopotassemia	S.T.; V.P.S.; V.Fib.	.....	.....	Serum K, 1.7 mEq./L.; died 5½ min. after acetyl strophanthidin (0.6 mg.)
18	49	Myocardial or pulmonary infarction, after gastrectomy for ulcer	I.V.R.	.....	.....	Sudden chest pain and shock 2 days after postoperative evisceration; died in ½ hr.
19	70	Pulmonary infarction ‡; ovarian carcinoma, metastatic	S.T.; V.P.S.; V.T.; I.V.R.; asystoles; I.V.R.	11, 16, 15	.....	Died 2 hr. after sudden dyspnea, shock, and air hunger
20	47	Myocardial infarction ‡	R.S.R.; V.P.S.; V.T.; V.Fib.	.....	.....	Sudden death during recording of ECG 3 hr. after onset
21	32	R.H.D.; pneumonitis	Asystole; I.V.R.; asystoles; V.T.	38, 13, 30, 6, 5, 9, 12, 14, 6, 9, 24, 24	Concussion; epinephrine; niketh-amide	ECG started after apparent death; electrical activity for over 15 min. more
22	38	Pneumonectomy for tuberculosis	Asystole; V.Fib.; I.V.R.; asystoles; I.V.R.	6, 5, 6, 4	Manual massage; procaine; epinephrine	Sudden cardiac arrest during operation; massage started at once
23	49	Pericardiectomy for constrictive pericarditis ‡	A.Fib.; A.Fl.; I.V.R.; asystole; I.V.R.	6	Intra-arterial transfusion; epinephrine	Died 7 hr. after operation
24	54	Myocardial infarction, cardiac rupture ‡	S.B.; I.V.R.; occasional P waves; asystoles; I.V.R.	6 (ventricular), 7, 9,	.....	Sudden collapse on bedpan on 5th day; ECG started when patient appeared dead
25	14	Massive aortic hemorrhage during ligation of patent ductus	S.T.; V.T.-V.Fl.; I.V.R.; A. Fib.; V.Fib.; A.Fl.-Fib.	.....	Procaine amide hydrochloride; epinephrine; pressure transfusion	Visual observation was asystole at time ECG showed V. Fib.; final deflections auricular
26	66	ASHD; Adams-Stokes syndrome	Complete A-V block; S.T.; V.P.S.; I.V.R.	.....	.....	Several Adams-Stokes attacks just before death; ECG ended within 1 min. of death
27	72	ASHD, after prostatectomy for hypertrophy	R.S.R.; N.R. or I.V.R.; V.T.; V.Fl.; V.Fib.	.....	.....	Acute pulmonary edema on 1st postoperative day; respiratory failure followed morphine (15 mg.)
28	69	Myocardial infarction	S.T.; incomplete A-V block, dropped beats; V.P.S.; V.T.; V.Fib.	.....	.....	Clinical death concomitant with onset of V. Fib.
29	50	Periarteritis nodosa ‡; HHD; uremia	S.B.; V.P.S.; S.V.T.; S.B.; Int. Dissoc.; N.R.; V.T.; V.Fib.	.....	.....	Sudden death; apparent death a few seconds before V. Fib.

*Summary of Cases *—Continued*

Case No.	Age	Diagnosis	Terminal Rhythms †	Length of Preterminal Asystoles, Sec.	Resuscitative Measures	Comment
30	54	Myocardial infarction; hepatic cirrhosis; avitaminosis	Complete A-V block; sinus slowing and arrhythmia; ventricular standstills; I.V.R.; V.P.S.; asystoles; I.V.R.	61, 30 (ventricular), 65, 5, 9, 15, 40, 60, 45	Concussion; epinephrine	Sudden death; electrical activity for more than 50 min. after apparent death
31	35	RHD; valvulotomy for mitral stenosis	A.Fib.; I.V.R.; V.P.S.; V.T.; V.Fib.	.....	Procaine; epinephrine; manual massage	Sudden appearance of intraventricular block at moment of finger-fracture of mitral valve
32	66	Peritoneal carcinomatosis	S.B.; sinus arrests; N.R.; asystole; I.V.R.	30	Intra-arterial transfusion	Sudden death
33	63	Carcinoma of pancreas; ASHD	A.Fib.; slowing of ventricular rate; ventricular standstills; persistence of ff waves	5, 9, 16, 20, 6, 30 (all ventricular)	.....	Sudden death; final deflections auricular (fibrillation)
34	58	Extensive coronary sclerosis; old massive myocardial infarct ‡	A.Fib. and I.V.R.; disappearance of ff waves; V.P.S.; bigeminy; asystoles; reappearance of ff waves; V.T.; I.V.R.	58, 9, 19, 10, 25, 28, 20	Epinephrine; ephedrine	Sudden death during routine ECG
35	65	Myocardial infarction ‡	I.V.R.; V.T.; I.V.R.	.....	.....	Sudden death 5 days after onset
36	8	Subendocardial fibrosis ‡	S.V.T. with BBB; I.V.R. with occasional P waves	.....	.....	Frequent attacks of paroxysmal tachycardia in preceding 4 yr.
37	56	Myocardial infarction	S.T.; asystoles; I.V.R.; asystoles; I.V.R.	31, 22, 18, 27, 36, 9, 40, 12, 25, 30	Concussion; epinephrine	Died 11 hr. after onset; many asystoles separated by only 1 or 2 ventricular complexes
38	59	Myocardial infarction	Asystole; I.V.R.; V.T.; ventricular standstill with A.F.; V.T.; I.V.R.	35, 8, 5, 20 (last 3 ventricular standstills)	Epinephrine	Electrical activity for 25 min. after clinical death
39	55	Myocardial infarction	V.P.S.; bigeminy; V.Fib.; V.Fl.; V.Fib.	.....	Intracardiac quinidine (0.2 gm.)	Sudden death during ECG recording 1¾ hr. after onset of chest pain
40	59	Pulmonary tuberculosis; cachexia	Complete A-V block; I.V.R.; asystoles; I.V.R.	9.5, 8.5	Epinephrine; concussion	Slow idioventricular rhythm for 15 min. after clinical death
41	62	Subarachnoid hemorrhage ‡	I.V.R.; asystoles; V.T.; extreme bradycardia	6, 5, 8	.....	Electrical activity for 12 min. after apparent death
42	62	ASHD; heart block with Adams-Stokes attacks ‡	Ventricular standstill; I.V.R.; A.Fib.	Duration unknown	Epinephrine	Final deflections auricular
43	64	ASHD; myocardial infarction ‡	S.T.; V.P.S.; V.T.; I.V.R.; asystoles; V.T.; I.V.R.	11, 9, 18, 12	.....	Convulsion during V. T.

† Unless otherwise stated, termination in each case was by slowing of the last rhythmic mechanism mentioned until final asystole.

* A. Fib. is auricular fibrillation; A. Fl., auricular flutter; ASHD, arteriosclerotic heart disease; A. T., auricular tachycardia; A-V, auriculoventricular; BBB, bundle branch block; HHD, hypertensive heart disease; Int. Dissoc., interference dissociation; I. V. R., idioventricular rhythm; N. R., nodal rhythm; N. T., nodal tachycardia; RHD, rheumatic heart disease; R. S. R., regular sinus rhythm; S. B., sinus bradycardia; S. T., sinus tachycardia; S. V. T., supraventricular tachycardia; V. Fib., ventricular fibrillation; V. Fl., ventricular flutter; V. P. S., ventricular premature systoles; V. T., ventricular tachycardia.

‡ Autopsy.

some works on medical history briefly mention an accidental human vivisection,[3] or the reappearance of signs of life [4] or a palpitating heart [5] in a deceased nobleman upon whose body Vesalius was performing an autopsy.

CLINICAL MATERIAL AND METHOD

Forty-three patients, ranging in age from 8 to 80 years, were studied. Heart disease was the primary cause of death in 25, of whom 17 had acute myocardial infarction. Other causes of death and additional data are set forth in the table.

Electrocardiograms were recorded for varying lengths of time before, during, and after death. In practically every case in which resuscitation was attempted, artificial respiration and oxygen administration, usually with pressure on the breathing bag, were also used. Resuscitative measures were applied in 22 cases. All references to drugs in the table alluded to intracardiac administration, mostly to the right of the sternum. The doses of epinephrine were 0.3 to 2.0 mg.; of nikethamide (coramine®), 250 to 500 mg.; of epinephrine, 0.15 to 0.30 mg ; of phenylephrine (neo-synephrine®) hydrochloride, 0.2 to 0.5 mg.; of procaine hydrochloride, 100 to 200 mg., and of procaine amide hydrochloride, 200 to 500 mg.

RESULTS

Electrocardiographic Changes.—1. Rhythm: Progressive disturbances in rhythmic mechanisms were present in all cases (Table). Idioventricular rhythm was the terminal mechanism in those cases in which ventricular fibrillation did not occur, except in Case 2 (Fig. 1). As death approached, the idioventricular pacemaker became irregular and slowed considerably. In some cases no more than two or three beats were present in the final minute prior to cessation.

Ventricular tachycardia occurred in nine cases without terminating in fibrillation. Ventricular fibrillation was the terminal mechanism in 10 cases and was transitory in 3 others. In only four cases was death judged to have occurred at the onset of ventricular fibrillation.

In 26 cases complete asystoles or standstills of the ventricles alone were observed prior to cessation. Asystolic periods varied in duration from 3 to 65 seconds and were usually multiple. In Case 21 there were 12 such asystoles recorded.

The very last complexes recorded were of ventricular origin in 38 cases. In the remaining five the final deflections after ventricular termination were those of auricular flutter, auricular flutter-fibrillation, auricular fibrillation, and auricular or sinus tachycardia.

2. The Ventricular Complex: As death approached the ventricular complex became increasingly aberrant and polymorphous, with ultimate shrinkage in amplitude and merging of the components into a broad monophasic curve. The only exception was Case 2, in which the final QRST complex was of normal form (Fig. 1). Deviations of the RS-T segment or junction were often seen, regardless of the underlying disease, and in three cases the deviations occurred in progressive fashion from beat to beat. Prominent U waves were not observed.

3. Garrison, F. H.: An Introduction to the History of Medicine, Philadelphia, W. B. Saunders Company, 1929.

4. Guthrie, D.: A History of Medicine, Philadelphia, J. B. Lippincott Company, 1946.

5. Mettler, C. C.: History of Medicine, Philadelphia, The Blakiston Company, 1947.

In three cases of bradycardia the Q-T intervals appeared too short for the slow rates (26 to 37 per minute). The values of K (Bazett) for these cases were 0.247, 0.267, and 0.283.

Resuscitative Attempts.—No improvement was noted which lasted longer than a few seconds, and there was no return of spontaneous respiration.

1. Epinephrine: Intracardiac injection during idioventricular rhythm was followed by ventricular extrasystoles (Case 23) and by auricular flutter with 2:1 and 3:1 auriculoventricular block (Case 25). After injection during asystole or ventricular standstill in nine patients, the following transient rhythms occurred: sinus tachycardia with complete auriculoventricular block, auricular flutter, ventricular extrasystoles, ventricular tachycardia, and idioventricular rhythm. In two other cases there was no effect.

2. Ephedrine and Nikethamide: Injection of each of these drugs was followed by resumption of idioventricular beats on one occasion.

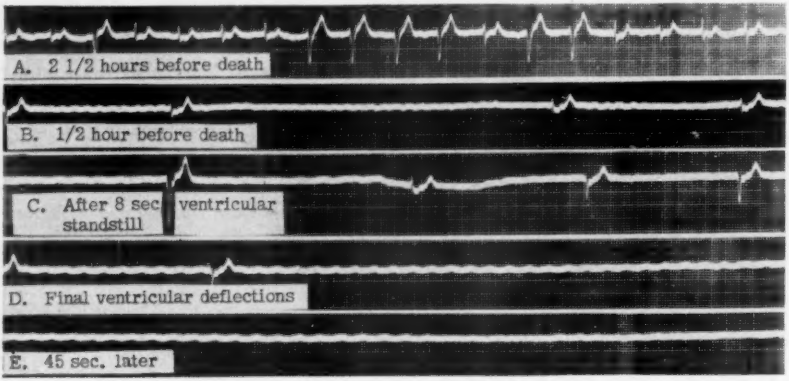
A. 2 1/2 hours before death
B. 1/2 hour before death
C. After 8 sec ventricular standstill
D. Final ventricular deflections
E. 45 sec. later

Fig. 1 (Case 2).—Lead II. Termination in auricular flutter. Note relatively normal form of the last ventricular complex, line *D*.

3. Procaine Hydrochloride: No effect was observed, even in a case in which the drug was injected directly into a coronary artery during operation. Procaine amide hydrochloride injected into the heart during ventricular tachycardia was followed in one case by idioventricular rhythm, alternating with undulatory ventricular tachycardia. In another case ventricular tachycardia was succeeded by idioventricular rhythm after intravenous administration of the drug.

4. Precordial Concussion: By this is meant a sharp or abrupt blow with the fist upon the lower sternum or precordium. This maneuver was followed by immediate resumption of the heart beat in each of three cases with asystole or ventricular standstill, but not in a fourth.

5. Intra-Arterial Transfusion: In one instance an asystole was followed by resumption of nodal rhythm 12 seconds after pressure in the apparatus was quickly raised to 120 mm. of mercury.

6. Manual Massage: In one case idioventricular rhythm succeeded ventricular flutter-fibrillation (or undulatory ventricular tachycardia) a few seconds after massage was started.

COMMENT

General Features of the Electrocardiogram of the Dying Heart.—The literature up to 1948 was reviewed by Stroud and Feil.[6] To their tabulation should be added several other publications.[7] Including the present report, I am aware of 44 papers on the subject, each dealing with 1 to 43 cases and describing a total of 288 dying human hearts.

From these reports certain common features are evident, some of which have already been summarized. In general, there is a slowing of sinus mechanisms, occasionally with sinus arrests, until some form of nodal rhythm supervenes. Various grades of auriculoventricular block may appear early. After a period of nodal rhythm, identifiable P waves disappear and the form of the ventricular complex becomes aberrant. The idioventricular rate slows, and the rhythm becomes increasingly irregular. The ventricular deflections become polymorphous and increasingly wide and shallow and, finally, cease altogether—sometimes suddenly and sometimes so insidiously that the exact moment of cessation cannot be determined. This pattern may be complicated by the appearance of all types of arrhythmias. Ventricular fibrillation is apt to occur after frequent ventricular extrasystoles, ventricular tachycardia, or prolonged asystole. Terminal mechanisms are largely independent of the underlying disease.

In animals differences in the modes of death due to anoxic anoxia, hemorrhagic shock, and coronary ligation have been noted.[8] The chief features were vagal effects,

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6. Stroud, M. W., and Feil, H. J.: The Terminal Electrocardiogram: 23 Case Reports and a Review of the Literature, Am. Heart J. **35**:910, 1948.

7. (*a*) Massie, E.; Huguley, C. H., and Stillerman, H. S.: The Heart in the Terminal State: Effect of Intracardiac Epinephrine, Ann. Int. Med. **29**:838, 1948. (*b*) Rohmer, H.: Über das Elektrokardiogram des Diphtherieherztodes, München. med. Wchnschr. **58**:2558, 1911. (*c*) von Hoesslin, H.: Zur Frage des langsamen und akuten Herztodes, Klin. Wchnschr. **3**:819, 1924. (*d*) Penati, F.: Elektrokardiographischer Befund von Herzflimmern bei plötzlichem Herztod, ibid. **12**:1249, 1933. (*e*) Tandowsky, R. M.; Anderson, N., and Vandeventer, J. K.: An Electrocardiographic and Clinical Study of Various So-Called Cardiac Drugs, Am. Heart J. **28**:298, 1944. (*f*) Enselberg, C. D.; Croce, J. P., Jr., and Lown, B.: Ventricular Fibrillation Due to Digitalis Preparations: A Review and Report of 2 Cases Following Intravenous Administration of Acetyl Strophanthidin, Circulation **3**:647, 1951. (*g*) Acierno, L. J., and Gubner, R.: Utility and Limitations of Intravenous Quinidine in Arrhythmias, Am. Heart J. **41**:733, 1951. (*h*) Levine, H. D.; Merrill, J. P., and Somerville, W.: Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man, Circulation **3**:889, 1951. (*i*) Kinsman, J. M.; Hansen, W. R., and McClendon, R. L.: Procaine Amide (Pronestyl) in the Treatment of Cardiac Arrhythmias, Am. J. M. Sc. **222**:365, 1951. (*j*) Cotrim, M. R.; Benchimol, A. B., and Schlesinger, P.: Coração agonizante: estudo electrocardiográfico de 8 casos, Arq. clín. **6**:61, 1948. (*k*) Meneses Hoyos, J.: Electrocardiogramme de l'agonie humaine, Arch. mal. cœur **43**:934, 1950. (*l*) Goldman, I. R.; Blount, S. G., Jr.; Friedlich, A. C., and Bing, R. J.: Electrocardiographic Observations During Cardiac Catheterization, Bull. Johns Hopkins Hosp. **86**:141, 1950.

8. Harris, A. S.: Terminal Electrocardiographic Patterns in Experimental Anoxia, Coronary Occlusion, and Hemorrhagic Shock, Am. Heart J. **35**:895, 1948.

pacemaker failure, and ventricular fibrillation, respectively. Changes due to vagal stimulation in anoxia and asphyxia have been observed by others.[9]

The role of potassium in the dying process may well be important, though it is difficult to assess. The well-known sequence of electrocardiographic changes in the dog heart in hyperpotassemia [10] may be duplicated in human subjects, even to ventricular fibrillation,[11] and may be simulated in human deaths not associated with known potassium disturbances. Whether the similarities are fortuitous or whether terminal hyperpotassemia actually plays a role in determining the terminal electrocardiogram is not known. It is known that in animals dying of various causes potas-

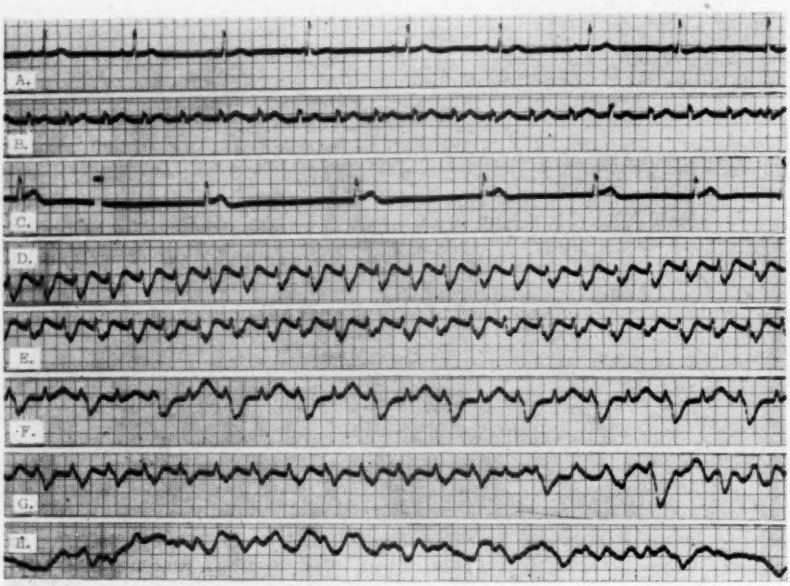

Fig. 2 (Case 29).—Lead II. Replacement of sinus rhythm by interference dissociation and nodal or His-bundle tachycardia (lines *A* and *B*). Nodal rhythm in line *C*. Lines *D*, *E*, and *F* are continuous, showing gradual development of bidirectional tachycardia involving S-T segments and T waves. Two or three seconds are missing between lines *F* and *G* and between lines *G* and *H*.

9. Gregersen, M. I., and Root, W. S.: Experimental Traumatic Shock Produced by Muscle Contusion with a Note on the Effects of Bullet Wounds: A Study of the Clinical Signs of Shock in the Dog and of the Role of Blood Volume Reduction in the Development of the Shock Syndrome, Am. J. Physiol. **148**:98, 1947. de Somer, E.: Manifestations ECG de l'asphyxie: L'alternant et l'extrasystole comme symptômes de transition: Electrocardiogramme, sans P ni T; Alternant ECG polymorphe; ECG expérimentale, Arch. internat. méd. expér. **13**:451, 1938.

10. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, J. Clin. Invest. **20**:607, 1941.

11. Levine and others.[7h] Marchand, J. F., and Finch, C. A.: Fatal Spontaneous Potassium Intoxication in Patients with Uremia, Arch. Int. Med. **73**:384, 1944. Elkinton, J. R.; Tarail, R., and Peters, J. P.: Transfers of Potassium in Renal Insufficiency, J. Clin. Invest. **28**:378, 1949.

sium may be liberated from the tissues in increasing amounts.[12] It is, therefore, conceivable that similar influences may operate in the last moments of human life.

Electrocardiographic Findings of Exceptional Interest in the Present Series.—In four cases (Cases 2, 12, 13, and 25) auricular flutter and fibrillation succeeded sinus rhythm, a sequence not previously observed.[7a] In nine cases ventricular tachycardia did not progress to fibrillation. This possibility is not well known, though it has been noted by others.[13]

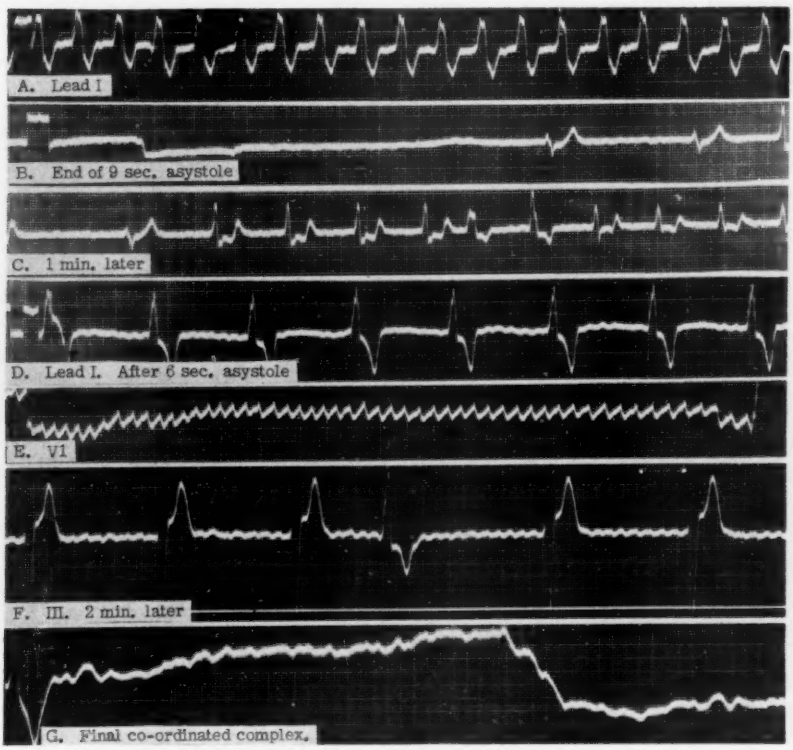

Fig. 3 (Case 3).—Lead II. Spontaneous ending of standstills of 9, 6, and 11.5 seconds. Note auricular flutter-fibrillation during ventricular standstill in line *E*. Final fibrillatory deflections in line *G* not affected by epinephrine or nikethamide injections.

An unusual type of ventricular tachycardia occurred (Case 29, Fig. 2), in which bidirectional alteration of T waves was the outstanding feature. This unique variety

12. Fenn, W. O.: The Role of Potassium in Physiological Processes, Physiol. Rev. **20**:377, 1940. Holmes, J. H.: The Relation of Serum Potassium to Shock in Dogs Subjected to Muscle Trauma, Am. J. Physiol. **148**:449, 1947. Burdette, W. J.: Studies on the Metabolism of Cardiac Muscle from Animals in Shock, Yale J. Biol. & Med. **23**:505, 1951.

13. Stroud and Feil.[6] Grieco, E. H., and Schwartz, S. P.: Observations on the Mechanism of the Dying Heart in a Patient with Ventricular Tachycardia, Am. Heart J. **16**:595, 1938.

of bidirectional ventricular tachycardia has not been hitherto described to my knowledge. Termination in ventricular fibrillation was not unexpected.[14]

In Case 3 ventricular fibrillation appeared unexpectedly [15] after a well-formed, though wide, QRST complex. It is possible that the final fibrillatory deflections in this case actually represent auricular rather than ventricular fibrillation (Fig. 3).[16]

Since termination of the ventricles before the auricles was first recorded [17] it has been found infrequently. There were five such instances in the present series, and possibly more could have been uncovered by using special exploratory leads for auricular activity.[18]

Asystoles have been observed in a minority of cases since their occurrence in the dying heart was first pointed out.[19] Their presence has not been stressed, and their

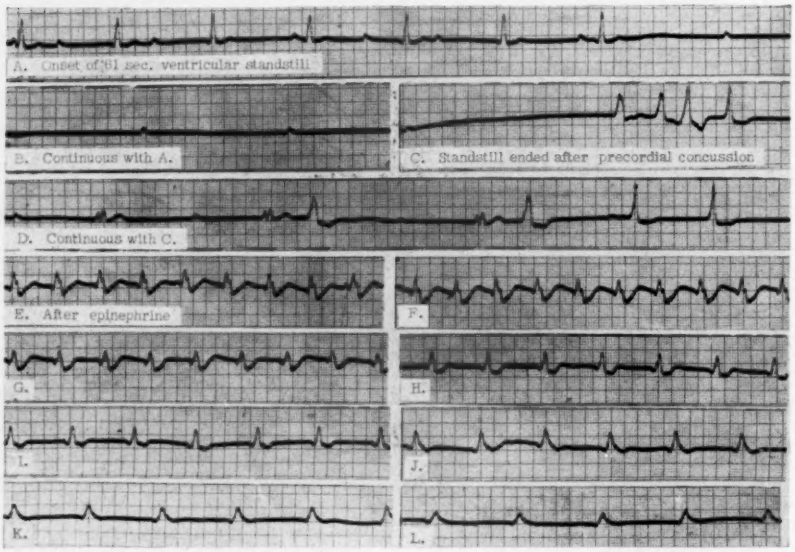

Fig. 4 (Case 30).—Lead II. Long ventricular standstill ended after precordial concussion. Other asystoles ended spontaneously, as well as after epinephrine injection. Lines *E* to *L* over a 10-minute period, with asystoles between them. Note progressive shifts of S-T segment. Line *L* followed by 45-second asystole ending in a single, final QRS complex.

14. Levy, A. G., and Lewis, T.: Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, Heart **3**:99, 1912.

15. Gallavardin, L.: La fibrillation ventriculaire, J. méd. Lyon **8**:453, 1927.

16. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, Am. Heart J. **20**:399, 1940.

17. Robinson, G. C.: A Study with the Electrocardiograph of the Mode of Death in the Human Heart, J. Exper. Med. **16**:291, 1912.

18. Enselberg, C. D.: The Esophageal Electrocardiogram in the Study of Atrial Activity and Cardiac Arrhythmias, Am. Heart J. **41**:382, 1951.

19. Willius, F. A.: Changes in the Mechanism of the Human Heart Preceding and During Death, M. J. & Rec. (Supp.) **119**:44, 1924.

frequency and duration have not often been stated. Complete cardiac asystole or standstill of the ventricles alone occurred in more than half my cases. Often there were several such periods in the same case. Most of them ended spontaneously, even after more than 30 seconds of arrest. It is possible that in many cases the recording of terminal electrocardiograms may have been stopped upon the appearance of a long asystole, before true cessation.

Since widening of the QRST complex is the usual finding, it was surprising to note three cases in which the Q-T interval was abnormally short for a time in the

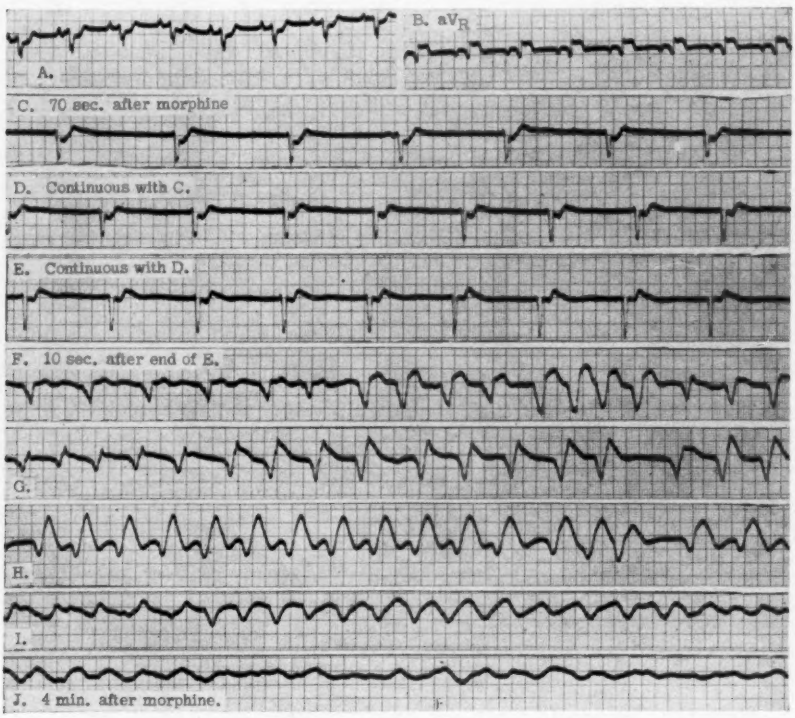

Fig. 5 (Case 27).—Lead II, except line *B*. Note progressive return to baseline of depressed S-T segment in lines *C*, *D*, and *E*. Development of ventricular fibrillation in lines *H*, *I*, and *J*.

moribund state. Granting that it may not be valid to express mathematically the correlation of Q-T intervals with long cycle lengths, and that changes in the intervals may be delayed for some seconds after changes in rate,[20] nevertheless, the observed intervals were so short as to be exceptional (corrected Q-T intervals of 0.247, 0.267, and 0.283 second). The paradox of extreme shortening of this interval, and, therefore, of electrical systole, during death cannot be explained. Perhaps it

20. Savilahti, M.: Untersuchungen über die QT-Dauer in Elektrokardiogramm, Acta med. scandinav. **121**:392, 1945.

represents the duration of electrical systole in only a portion of myocardium, the rest being inactive; or perhaps there may be a state of supernormal excitability due to unusual changes in myocardial metabolism.

Progressive deviations of the RS-T junction or segment from beat to beat have not previously been noted. Examples are seen in Figures 4 and 5. The most striking shifts were in Case 19 (Fig. 6), in which several migrations up to 6 mm. occurred! These shifts are probably reflections of progressive alterations in the rate and manner of repolarization paralleling temporary bettering and worsening of metabolic processes in the dying myocardium.

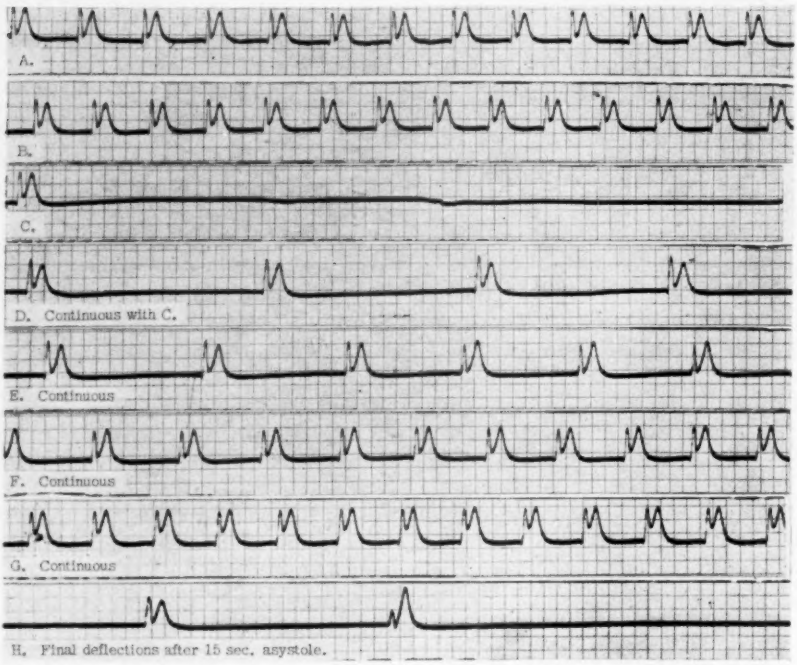

Fig. 6 (Case 19).—Lead II. Proved case of pulmonary embolism from femoral vein thrombus. Note progressive elevation of RS-T junction in lines *A* to *C*; progressive decline in lines *D* and *E*, and elevation again in lines *F* and *G*.

Resuscitative Measures.—Obviously a study of only fatal cases is not ideal for evaluating the efficacy of resuscitative measures. Nevertheless, a most remarkable paper on the subject was based on a study of resuscitation of hearts already dead. Kountz [21] devised an apparatus for independent perfusion of the coronary arteries and the left ventricle. With this he was able to restore ventricular contraction in 65 of 127 human hearts, in five minutes to six hours after death. In 48 of them regular beating for at least two hours was produced.

21. Kountz, W. B.: Revival of Human Hearts, Ann. Int. Med. **10**:330, 1936.

In the present study the frequency of asystoles, many of which were apparently self-limited, tends to throw at least some doubt upon the effectiveness of restorative measures followed by resumption of heart beats. This is especially vexing in the case of intracardiac administration of epinephrine. Most of the reported cases, including my own, have no record of the exact time relations between the injection and the return of heart beats. Thus, it is most difficult to exclude the possibility of independent resumption of cardiac activity. Only if cardiac activity occurs immediately after injection should it be attributed to the epinephrine (Fig. 7).

The status of intracardiac administration of epinephrine is clouded. Hyman [22] concluded, after reviewing 250 cases with 25% successes, that it was the mechanical action of the needle puncture rather than the drug which was effective, and that

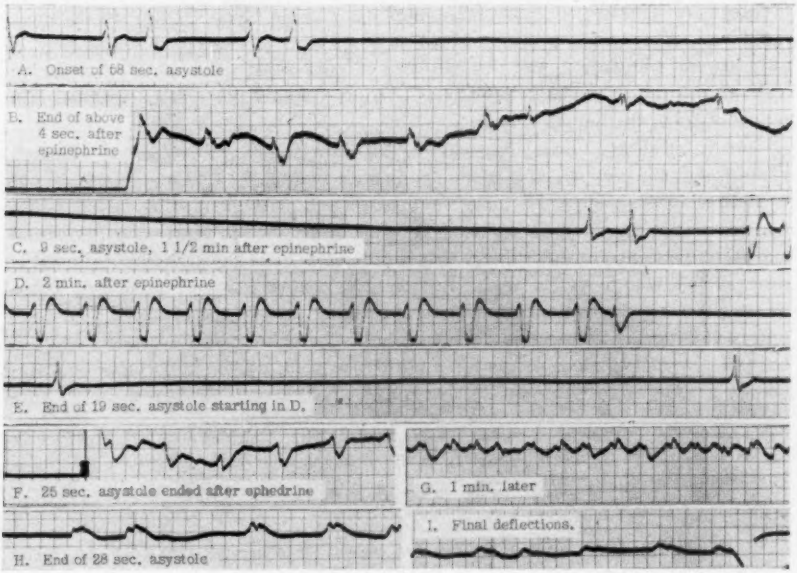
A. Onset of 68 sec. asystole
B. End of above 4 sec. after epinephrine
C. 9 sec. asystole, 1 1/2 min after epinephrine
D. 2 min. after epinephrine
E. End of 19 sec. asystole starting in D.
F. 25 sec. asystole ended after ephedrine
G. 1 min. later
H. End of 28 sec. asystole
I. Final deflections.

Fig. 7 (Case 34).—Lead II. Long asystole presumably ended by intracardiac administration of epinephrine. Some asystoles ended spontaneously (lines *C* and *E*).

ectopic beats and arrhythmias were so frequent that the puncture should be made into the right auricle rather than into either ventricle. The occurrence of ventricular fibrillation after intracardiac injection of epinephrine is common,[23] though it does not always follow.[24] Moreover, other and safer measures, such as the maintenance of

22. Hyman, A. S.: Resuscitation of the Stopped Heart by Intra-Cardiac Therapy, Arch. Int. Med. **46**:553, 1930.

23. Massie and others.[7a] Willius.[19] Wiggers, C. J.: The Physiologic Basis for Cardiac Resuscitation from Ventricular Fibrillation: Method for Serial Defibrillation, Am. Heart J. **20**:413, 1940.

24. Levine, S. A., and Matton, M.: Observations on a Case of Adams-Stokes Syndrome, Showing Ventricular Fibrillation and Asystoles Lasting 5 Minutes, with Recovery Following

(Footnote continued on next page)

respiration and oxygenation and of the blood volume, are probably at least as useful. My own results with intracardiac administration of epinephrine were not particularly promising, nor were the results with the other drugs injected directly into the heart.

The use of precordial concussion has been mentioned by others.[25] It is an inelegant form of mechanical stimulation, and it can hardly be expected to yield lasting results. After this maneuver several asystoles ended immediately in one of my cases (Fig. 4), and single asystoles stopped in two other cases.

Measures to support the blood volume and pressure not only are physiological and safe but are fundamentally necessary in resuscitation. Systematic studies in animals have shown that the best empirical guide to revivability is the blood pressure, and that below critical systolic levels resuscitation is impossible.[26] It may even be necessary to resort to intracardiac administration of blood.[27] In man the most rapid way of restoring systemic blood pressure and increasing coronary flow is intra-arterial transfusion, and this has been recommended when other resuscitative methods are not immediately effective.[28] In my Case 32 this method resulted in a return of nodal rhythm after asystole.

The value of direct manual massage of the heart is universally accepted, although by itself it is not very effective in maintaining circulation.[29] Maximal effects cannot be attained unless the blood volume is supported, and massage must be started within five minutes of circulatory arrest.[30] The value of massage in ventricular fibrillation has been questioned on the ground that it may perpetuate the arrhythmia, and it is probable that electric defibrillation is required to restore activity,[31] though occasionally manual massage and administration of procaine may be successful.[32] The function of massage is to maintain circulation while other measures are being applied. Several reported cases of successful defibrillation point up the importance of maintaining a state of readiness to deal with this emergency.[33] In two instances suc-

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the Intracardiac Injection of Adrenalin, Heart **12**:272, 1926. Melville, K. I.: Further Studies on the Antifibrillatory Action of Coronary Dilator Drugs in Chloroform-Adrenaline Ventricular Fibrillation, Am. Heart J. **37**:651, 1949.

25. Hyman.[22] Battro, A.: Las arritmias en clínica, Buenos Aires, Libreria y editorial "El Ateneo," 1948.

26. Swann, H. G., and Brucer, M.: The Sequence of Circulatory, Respiratory and Cerebral Failure During the Process of Death: Its Relation to Resuscitability, Texas Rep. Biol. & Med. **9**:180, 1951.

27. Fauteux, M.: Cardiac Resuscitation, J. Thoracic Surg. **16**:623, 1947.

28. Hanks, E. C., and Papper, E. M.: Cardiac Resuscitation, New York J. Med **51**:1801, 1951.

29. Beck, C. S., in Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease, Ed. 3, Philadelphia, F. A. Davis Company, 1945, Vol. 2. Johnson, J., and Kirby, C. K.: An Experimental Study of Cardiac Massage, Surgery **26**:472, 1949.

30. Levy, A. G.: Massage of the Fibrillating Ventricles, Heart **7**:175, 1920.

31. Wiggers.[16] Fauteux.[27]

32. Johnson, J., and Kirby, C. K.: Cardiac Resuscitation, J. Mt. Sinai Hosp. **18**:141, 1951.

33. Hanks and Papper.[28] Beck, C. S.; Pritchard, W. H., and Feil, H. S.: Ventricular Fibrillation of Long Duration Abolished by Electric Shock, J. A. M. A. **135**:985, 1947. Ruzicka, E. R., and Nicholson, M. J.: Cardiac Arrest Under Anesthesia, ibid. **135**:622, 1947. Lampson, R. S.; Schaeffer, W. C., and Lincoln, J. R.: Acute Circulatory Arrest from Ventricular Fibrillation for 27 Minutes with Complete Recovery, ibid. **137**:1575, 1948. Johnson, J., and Kirby, C. K.: Cardiac Resuscitation, S. Clin. North America **29**:1745, 1949.

cesses were achieved in apparent sudden death of two patients who were not at the time undergoing surgical procedures and in whom immediate surgical exposure of the heart and institution of resuscitative measures were done.[34] It is to be hoped that less drastic methods may be evolved, such as the application of electric impulses through a cardiac catheter [35] or even simpler procedures.

SUMMARY AND CONCLUSIONS

The electrocardiographic features of the dying human heart were studied in 43 cases. Though all types of arrhythmias may occur, the terminal electrocardiogram generally follows a broad pattern unrelated to the underlying disease. Characteristically, lower pacemakers predominate until irregular idioventricular rhythm with gradual slowing appears. Termination in ventricular fibrillation occurs in a minority of cases (1/5 to 1/3).

Recurring asystoles or ventricular standstills are common and often appear to be self-limited.

The following unusual, or hitherto unreported, findings were described: (1) auricular flutter and fibrillation succeeding sinus rhythm (four cases); (2) bidirectional ventricular tachycardia with alternation of RS-T segment and T waves only (one case); (3) paradoxical shortening of the Q-T interval (three cases), and (4) progressive shifts of RS-T junction and segment (three cases).

Resuscitative measures used in 22 cases are discussed. The difficulty of their evaluation, in view of the frequency of recurring self-limited asystoles, is stressed.

It is concluded that the intracardiac use of epinephrine should be avoided until other measures have been exhausted. These include intravenous and intra-arterial blood transfusion and artificial respiration with oxygen. Resuscitation from ventricular fibrillation requires immediate surgical exposure for the purpose of manual cardiac massage and electric defibrillation, together with procedures to support blood pressure and respiration.

34. Southworth, J. L.; McKusick, V. A.; Pierce, E. C., II, and Rawson, F. L.: Ventricular Fibrillation Precipitated by Cardiac Catheterization, J. A. M. A. **143**:717, 1950.

35. Callaghan, J. C., and Bigelow, W. G.: An Electrical Artificial Pacemaker for Standstill of the Heart, Ann. Surg. **134**:8, 1951.

SPONTANEOUS CHYLOTHORAX

Observations on Its Pathogenesis and Management Based on Study of Five Cases

RICHARD H. MEADE, M.D.
GRAND RAPIDS, MICH.

CHYLOTHORAX is still a relatively rare condition, but, since Lampson in 1946 successfully treated a patient with this condition by intrathoracic ligation of the thoracic duct, it has been shown that chylothorax in itself should never be fatal. Many excellent articles on the subject of traumatic chylothorax have appeared in recent years. When Lampson [1] published his article in 1948, he had been able to collect reports on only 58 cases of traumatic chylothorax from the world's literature. More cases due to malignant disease and vascular disturbances have been reported, but very few cases of so-called spontaneous origin have been recorded. As I have observed five cases of the last type in the past four years, and these have shown a striking similarity in etiological factors, it seems worth while to present them and to discuss their pathogenesis and management.

That chylothorax occurs without any previous obvious injury is well known. Various factors have been considered as of importance in its pathogenesis, but no attempt has been made to correlate them. In the five cases to be presented here, there was one factor common to all five, and another factor was found in four. A hypothetical third factor is believed to be necessary. These three factors will be discussed and the treatment of the condition summarized.

SUMMARY OF CASES

The first patient was a young woman of 24, who entered Wesley Memorial Hospital, Chicago, in March, 1947, on the service of Dr. Paul Rhoads because of a left pleural effusion. This fluid was found to be chyle. Three weeks before the development of symptoms of the effusion, she had fallen down her cellar steps without any apparent ill-effects. During a period of nine weeks repeated aspiration of the chyle was done, and extensive studies were carried out to determine the cause of the chylothorax, but without success. Having learned of Lampson's successful ligation of the thoracic duct in a similar case, this was planned for her. At the operation a fistula in the mediastinal pleura, from which chyle escaped, was found just below the lower margin of the inferior pulmonary ligament. The tissues in this area were indurated, so no attempt was made to isolate the duct here, but it was exposed lower down and ligated with two fine silk ligatures. The hilar part of the lung was infiltrated with chyle, and the lung was held in a partly collapsed state by an inflammatory membrane. Decortication of the lung could be successfully done only to the extent of allowing the lung to be inflated to three-fourths of its normal size. Closed drainage of the pleural cavity for two days allowed the lower two-thirds of the lung to reexpand fully, but complete obliteration of the pleural space did not occur until six weeks later. She had no further escape of chyle and left the hospital three weeks after the operation in good condition. For more than three years she remained in good health, except

Read before the meeting of the Chicago Surgical Society, Nov. 2, 1951.

1. Lampson, R. S.: Traumatic Chylothorax: A Review of the Literature and Report of a Case Treated by Mediastinal Ligation of the Thoracic Duct, J. Thoracic Surg. **17**:778, 1948.

for a chronic cough. In January, 1951, dyspnea developed and she was found to have a right chylopneumothorax. The left chest, the site of the original chylothorax, was apparently normal. Suction drainage of the right pleural cavity resulted in reexpansion of the lung within three weeks, and she again left the hospital in good condition, but with some dyspnea on exertion. Since then she has had three more attacks of right spontaneous pneumothorax, and the dyspnea has increased. She now has evidence of diffuse emphysema of her right lung.

Roentgenograms of this patient's back showed evidence of congenital anomalies of the upper dorsal vertebrae, there being hemivertebrae and some scoliosis. It is thought that other changes lower down could have caused fixation of the thoracic duct and that, when she fell down the steps, there was sudden hyperextension of the back, with rupture of the stretched duct.

The second patient was a woman aged 58, who also was admitted to Wesley Memorial Hospital, Chicago. She entered the hospital on the service of Dr. Gilbert Marquardt, June 18, 1947, because of shortness of breath and pains in the middle of the back on deep breathing. She was found to have a right chylothorax. She had fallen down some steps six months prior to her entry into the hospital without any apparent injury. After a thorough study to determine the cause of her chylothorax had failed, she was operated upon on July 30 through the right chest, and what was thought to be the thoracic duct was resected along with some of the adjacent tissue. Closed drainage of the pleural cavity for two days resulted in complete reexpansion of the lung, but chyle appeared in the opposite side of the chest. The structure resected at operation proved to be the lesser splanchnic nerve. The adjacent tissue showed evidence of marked chronic inflammation. As the chyle leakage persisted in spite of repeated aspiration of it, she was again operated upon 17 days later through the right chest. This route was chosen in spite of absence of chyle in this side because it was considered to be the side of the rupture, the chyle passing through the opening in the right pleura made at operation, and there being no free pleural space left in the right chest because of the complete expansion of the lung. This situation was found, and the lung had to be peeled from the anterior surface of the vertebrae where the duct was thought to be. A most exhaustive search revealed only one small lymph channel; so the chest wall was again closed with underwater drainage. Tissue removed at this stage again showed evidence of a severe chronic inflammatory process. The lung again promptly reexpanded, but chyle appeared in the left pleural cavity. Four days after this operation chyle was again aspirated, and this was done repeatedly for another month. Simple catheter drainage was then established on the left, and within one week the flow of chyle ceased. The tube was then removed, and the patient had no further chylothorax. She was finally discharged from the hospital on Oct. 11, almost four months after her admission.

This patient remained well until January, 1948, when a dry cough and a severe dermatitis developed. She was readmitted to the hospital on Jan. 12; jaundice developed two days later, and she died within two days of fulminating hepatitis. At autopsy it was found that she had a small amount of chyle in each pleural cavity, but no trace of a thoracic duct could be found after an exhaustive search. There was an extensive flat growth of tissue throughout the posterior mediastinum and the retroperitoneal area. This proved to be lymphosarcoma (lymphocytoma). This tissue was also seen in the lungs, liver, gall bladder, pancreas, kidneys, ovaries, bone marrow of the vertebral bodies, mesenteric fibroadipose tissue, and the lymph nodes. She had acute necrosis of the liver and edema of the brain, which were thought to be the causes of her death. The hepatitis was thought to be of the homologous serum type, in view of the numerous transfusions and plasma infusions she had had during her stay in the hospital before the chylothorax was controlled. It was thought that she had many fine chyle channels, as described by Davis [2] in 1915, and that these had become fixed to the vertebral column by the inflammatory tissue which had preceded the development of the lymphosarcoma. The fall which she had had was thought to have caused sudden hyperextension of her back with rupture of one or more small ducts. Because of the small size of these ducts, chyle was slow to appear in the pleural cavity.

The third case was that of a 35-year-old graduate nurse, who began having deep-seated pain and a heavy sensation in her right upper abdomen four days after doing a number of back dives. She had not been accustomed to making such dives. The pain was accentuated on deep breathing and on coughing. A week later the pain was more pronounced in the right lower chest,

2. Davis, H. K.: A Statistical Study of the Thoracic Duct in Man, Am. J. Anat. **17**:211, 1915.

and she stopped work. As there was no improvement after a week, she had a cholecystogram made, with normal findings, and then three days later a chest roentgenogram showed evidence of a right pleural effusion. She was admitted to Butterworth Hospital, Grand Rapids, Mich., on Aug. 25, 1949, and aspiration of her chest showed the fluid to be chyle. She was then referred to me by her physician, Dr. H. E. Veldman. The chyle was aspirated on four successive days without decrease in amount, and, accordingly, closed drainage of the right pleural space was instituted. Reexpansion of the lung and cessation of chyle drainage occurred within one week. After withdrawal of the drainage tube, there was some persistence of loculated fluid for several weeks, but no further leakage of chyle was evident. She has remained perfectly well during the two years since then. Fixation of her thoracic duct to the vertebral column was apparently due to an old injury to her back, which she does not remember but roentgen-ray evidence of which was first found in 1943 when she entered the Army Nursing Corps. The roentgenogram revealed wedging of the seventh dorsal vertebra. The back diving, to which she was not accustomed, could have caused rupture of the fixed duct by sudden hyperextension.

The remaining two patients were not under my care but were seen on visits to Boston and to Ann Arbor, Mich. The first was seen at the Boston City Hospital, on the service of Dr. Theodore I. Badger, in October, 1949. She was an 18-year-old girl who had been admitted to the hospital on June 5 because of a left pleural effusion, associated with cough, exertional dyspnea, and anorexia. She had been in the hospital on two occasions in 1948 because of congenital heart disease and microcytic hypochromic anemia. On the occasion of her June admission the pleural fluid was found to be chyle, but after several aspirations she was discharged to the outpatient department. However, she was readmitted in July, and aspirations of the chyle continued with no improvement. In October she was transferred to the service of Dr. John Strieder, and catheter drainage of the pleural cavity was instituted. Difficulty was experienced in maintaining drainage, but on the 10th day the catheter was removed, as there seemed to be no further leakage of chyle. Two further thoracenteses were necessary because of small remaining pockets of chyle, but after this there was no further evidence of chylothorax, and she was discharged from the hospital. She was last seen in February, 1950, three months after her discharge from the hospital, and there had been no further evidence of chylothorax. Efforts to trace her since then have not been successful.

In this case the pathogenesis of the chylothorax is less obvious. At the age of 3½ years the patient had had a severe back injury resulting from an automobile accident, with paralysis of her legs for three weeks and weakness in them for nine months. Roentgenograms of her chest taken in the hospital in 1948 were interpreted as showing a scoliokyphosis in the dorsal and lumbar regions. This injury could certainly have produced enough changes about her thoracic duct to cause its fixation to the underlying vertebrae. In spite of careful questioning, no history could be elicited of a recent fall or other cause of sudden hyperextension of the back, which might have resulted in rupture of the thoracic duct. It is assumed, however, that such an incident may have occurred without notice. No other cause of the chylothorax could be found.

The other patient with chylothorax who was seen but was not under my care was a 41-year-old acrobat who entered the University of Michigan Hospital, in Ann Arbor, on April 30, 1951, because of a left pleural effusion. He had had a severe stricture of his esophagus following an attempt at suicide by swallowing potassium hydroxide in 1948. A gastrostomy had been done, and dilatation of the strictured esophagus was carried out until the patient was able to do it himself. Stenosis of his pylorus had also developed, and this required gastroenterostomy. He had several attacks of periesophagitis. On entry into the hospital because of his pleural effusion, his esophagus was no longer causing trouble. Prior to the discovery of the pleural effusion he had pain in his left chest, dyspnea on exertion, and a cough. The fluid was found to be chyle, and it was aspirated several times without any diminution in the amount in the chest. Suction drainage was started, and the lung seemed fully expanded. It was thought that the leakage of chyle had stopped; so he was discharged from the hospital. However, he began coughing up chyle soon after this and was readmitted to the hospital on July 31, three days after he started to expectorate the chyle. It was decided that ligation of the duct was necessary. On Aug. 8, Dr. Herbert Sloan approached the duct through the right chest and ligated it a short distance above the diaphragm. After this the patient made a smooth recovery, and when last seen on Sept. 29 his condition was good.

Before it was discovered that this man had a pleural effusion, he had done a number of back flips, to which he had been unaccustomed for some time; at first he had a dull, deep-seated pain in the left lower chest and occasional sharp pains in the left axilla. Discovery of the chylothorax followed. In this case there was sudden hyperextension of the back after the duct could have become fixed to the vertebrae as a result of the attacks of periesophagitis.

COMMENT

Pathogenesis.—Five cases are presented as examples of so-called spontaneous chylothorax. Each developed without evidence of any obvious, direct, traumatic origin, although in four of the five there was a previous incident in which there could have been sudden hyperextension of the back. The normal thoracic duct is a slender, but fairly strong, vessel which is deeply placed in the body over the anterior surfaces of the dorsal vertebrae. It is held in place by a rather large amount of areolar tissue which allows it to move freely with movements of the vertebrae. It is inconceivable that it could be overstretched and ruptured by any vertebral movement, unless it had become fixed to the vertebrae. In each of the five cases presented there was evidence that the duct could have become fixed as a result of congenital anomaly, trauma, or infection.

In the first case there was roentgen-ray evidence of a congenital anomaly of the dorsal vertebrae. Associated with this obvious abnormality, there may have been other changes which caused fixation of the thoracic duct. In the second case there was histological evidence of a marked chronic inflammatory process in the region of the only thoracic duct found in the patient. The fact that a definite widespread lymphosarcoma developed in this area later does not invalidate the concept of the duct, or ducts, having become fixed prior to their rupture. In the third case there was roentgen-ray evidence of an old fracture of a dorsal vertebra, and in the fourth case there was the history of a severe back injury in childhood. In the last case infection in the region of the thoracic duct could easily account for its fixation. It seems, therefore, that one of the essential factors for subsequent rupture of the thoracic duct was present in each of the five cases.

The second factor thought to be if importance is the sudden overstretching of the previously fixed duct. A definite history of this was obtained in all except one case. The first two patients fell down steps at varying intervals before the appearance of the chylothorax. In the first the interval was only three weeks. In the second there was an interval of six months, but, in studying her history carefully, one finds that she had various indefinite symptoms for several months before a pleural effusion became evident. As she had no single, normal-sized duct, rupture of one small one could mean slow leakage of chyle into the mediastinum for a long time before there was enough pressure to cause a rupture of the pleura with escape into the pleural cavity. The third patient did some back dives to which she was unaccustomed and within four days had symptoms which were later found to be due to rupture of the thoracic duct. In the fourth patient no history of any fall or sudden movement which might have caused a rupture of the duct could be elicited. The fifth patient, an acrobat out of practice for a long time, did some back flips, with development in a few days of pain in the chest, dyspnea, and a cough.

Although it might seem that any thoracic duct could be ruptured by overstretching if a portion of it is fixed to the vertebrae, this apparently is not true. Certainly, there are thousands of accidents each year in which vertebrae are badly injured, and

among persons with such injuries must be many in whom there is enough trauma in the region of the thoracic duct to cause some fixation of it in scar tissue. Among these persons there must be many who subsequently suddenly hyperextend their backs. In spite of these observations, the number of cases of spontaneous chylothorax that are recognized is very small. The only explanation for this discrepancy seems to be that a third factor is necessary to cause a rupture of the duct. This factor is believed to be an increased fragility of the ductal wall, due possibly to the agent causing the fixation of the duct or to something else.

It is clearly realized that this attempted explanation of the pathogenesis of the chylothorax in these five cases is based entirely on history, clinical observation, and speculation. The thoracic duct has received little attention in the past from pathologists, anatomists, or clinicians. Diseases affecting the duct are apparently rare, and few pathologists have routinely examined the duct at autopsy. Rupture of the duct from trauma had been infrequently discussed in the literature until the successful transthoracic ligation of the duct was reported in 1948.[1] Chylothorax resulting from involvement of the duct by malignant disease has been discussed even less often, apparently because of the hopeless nature of the underlying process. In order to test the soundness of the hypothesis advanced above, efforts should be made to study the problem in the experimental animal, and it is hoped that this may be done. Although the five cases which have been presented here seem to fit into a definite group, it is not presumed that all cases of apparently spontaneous chylothorax are due to these factors. A sudden increase in intraductal pressure, as the result of coughing or other incident, may be the precipitating factor in some cases, and there may be other factors in other cases. It is believed, however, that the causes presented in the five cases reported here are the commonest.

Treatment.—Numerous authors in excellent articles published in the last few years have discussed the treatment of chylothorax.[3] Since Lampson's demonstration of the effectiveness of ligation of the thoracic duct above the diaphragm, most authors have reported their experiences with this procedure. In this connection it is interesting to recall that Lilienthal,[4] in his book on thoracic surgery published in 1925, had this to say about the treatment of traumatic chylothorax:

> When there is rapid emaciation and it becomes manifest that the wound will not close spontaneously, wide thoracotomy may be indicated with a search for the wound in the duct, which may then be ligated, or otherwise dealt with. The chances are good that the rich anastomosis will furnish a new channel into the venous circulation.

Although he published this statement in 1925, he apparently never had the opportunity of putting his plan into effect. As far as is known, no one else did so until Lampson operated on his patient 21 years later. That the operation will almost invariably succeed has been well attested to by various reporters, and it is now fully accepted. When a single thoracic duct exists, as is true in the great majority

3. (*a*) Lampson.[1] (*b*) Baldridge, R. R., and Lewis, R. V.: Traumatic Chylothorax: A Review of the Literature and Report of a Case Treated by Ligation of the Thoracic Duct and Cysterna Chyli, Ann. Surg. **128**:1056, 1948. (*c*) Hodge, G. B., and Bridges, H.: Surgical Management of Thoracic Duct Injuries: Experimental Study with Clinical Application, Surgery **24**:805, 1948. (*d*) Meade, R. H.; Head, J. R., and Moen, C. W.: The Management of Chylothorax, J. Thoracic Surg. **19**:709, 1950.

4. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925, Vol. 1, p. 527.

of cases, the operation is not a difficult one, but it is a major procedure and should not be undertaken lightly. Simpler means of controlling chylothorax have proved successful in many cases. Indeed, it has been generally stated that about half of the cases of chylothorax will clear with simple, repeated aspiration of the chyle. In the cases in which success was reported prior to 1948 treatment in all was by simple aspiration. Because of this observation, it is obviously wise to start treatment in every case of chylothorax in this way. In some it will be immediately evident that aspiration will not suffice. Then one should resort to closed drainage of the chylothorax, with or without suction. In no case should simple aspiration of the chyle be prolonged more than a few days, unless there is evidence of rapid decrease in the amount of the fluid. In three of the above cases closed drainage was effective. In the second case there was a beautiful demonstration of the effectiveness of simple underwater drainage in enabling the lung to obliterate the pleural cavity promptly and completely. In the first case such drainage could not have been effective at the time of the operation, because the lung had become collapsed and was prevented from reexpansion by an inflammatory membrane. Had this form of treatment been instituted in the early phase of the chylothorax, it probably would have worked well. In the last case the lung was prevented from completely obliterating the pleural space by adhesions from earlier infection that had walled off the area into which the chyle escaped. Certainly ligation of the thoracic duct should be done unless simpler measures have proved effective, and it should not be postponed indefinitely. The object of closed drainage is to obliterate the space into which the chyle escapes by sealing the opening with healthy lung, rather than to allow the injured duct to heal by relieving pressure on it.

Concerning the ligation of the duct, when it is decided to be necessary, two points are worth mentioning. If there is a choice of sides through which to approach the duct, approach through the right thorax is much easier than that through the left. The patient should be in the supine position or rolled slightly to the left. Access to the anterior surfaces of the lower dorsal vertebrae is easy. The duct will be found between the azygos vein and the aorta just medial to the lesser splanchnic nerve. Care must be taken not to mistake the nerve for the duct. The duct is smaller and tenuous, and the presence of valves is apparent. If cream or a lipophylic dye [5] has been given before the operation, the duct will be much more prominent. If the chylothorax involves the left chest and the lung is so collapsed that a contralateral pneumothorax would not be tolerated, then the duct must be approached through this side. Here again the patient should be in the dorsal decubitus position. On this side the esophagus has to be retracted medially and the aorta laterally; then the duct is found after dissecting the areolar tissue over the vertebrae. In the first case reported here the duct was doubly ligated with silk, but was not sectioned. Three years later chylothorax developed in the opposite side of the chest. This would seem to indicate that there had been restoration of the continuity of the duct, although it is possible that the patient may have ruptured some collateral channel. However, it would seem wiser to resect a small segment of the duct, for then histological examination of it could be done and the possibility of recanalization is precluded. In the second case such a procedure quickly and surely demonstrated my mistake in identification of the duct. After the resection of the duct, closed

5. Klepser, R. G., in discussion on Meade and others.[3d]

drainage of the pleural cavity should be established, as is usually done after thoracotomy, so as to ensure rapid reexpansion of the lung and obliteration of the pleural space.

During the period before the leakage of the chyle can be stopped, it will be necessary to supplement the patient's diet by additional protein and fat. If intravenous administration becomes necessary, it would seem wise to use protein hydrolysates and whole blood rather than plasma, as by the use of the latter homologous serum jaundice may be induced. Although it would seem logical to reinfuse the chyle, and a number of successful cases of reinfusion have been recorded, there have been at least two fatalities reported which seemed to have been due to the infused chyle.[6] Until the safety of this agent can be determined by animal experiments, this method should not be used. As the period during which this augmentation of the diet is necessary should be short, no great problem is presented by it.

SUMMARY AND CONCLUSIONS

Five cases of chylothorax not due to any direct trauma or to other obvious cause are presented. In each of them there was evidence of some previous condition which could have caused fixation of the thoracic duct to the vertebrae. In four of the five there was a history of some subsequent sudden movement that could have caused hyperextension of the vertebral column. It is believed that these two factors are insufficient in themselves to cause rupture of the duct and that a third one is necessary. This third factor, purely hypothetical, is increased fragility of the thoracic duct. This could be due to the same cause that produced fixation of the duct, or to some other factor.

Two of the five patients were successfully treated by ligation of the thoracic duct just above the diaphragm. Three were successfully treated by closed drainage of the chylothorax. In the first patient, whose duct was ligated, a contralateral chylopneumothorax developed three years later which responded to closed drainage. The second patient, whose chylothorax was controlled by closed drainage after two unsuccessful attempts to find and ligate the thoracic duct, died as a result of fulminating hepatitis after five months and was found at autopsy also to have a widespread lymphosarcoma.

In the treatment of chylothorax, simple aspiration should be tried first for a few days. If no real improvement results, closed drainage should be established and tried for a week. Failure of this procedure requires operation on the thoracic duct. Resection of a portion of the duct and ligation of the ends should be done, rather than simple ligation alone. It is hoped that in the future efforts will be made to resect the injured part of the duct, so that more information about the causation of chylothorax may be obtained.

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6. Peet, M. M., and Campbell, K. N.: Massive Chylothorax Following Splanchnicectomy, Univ. Hosp. Bull., Ann Arbor **9**:2, 1943. Whitcomb, B. B., and Scoville, W. B.: Postoperative Chylothorax, Arch. Surg. **45**:747, 1942.

ENDEMIC INFECTIOUS HEPATITIS IN AN INFANTS' ORPHANAGE

II. Epidemiologic Studies in Infants and Small Children

ALFRED M. BENNETT, M.D.
RICHARD B. CAPPS, M.D.
CHICAGO
MYLES E. DRAKE, M.D.
PHILADELPHIA
RICHARD H. ETTINGER, M.D.
ELIZABETH H. MILLS, M.S.
CHICAGO
AND
JOSEPH STOKES Jr., M.D.
PHILADELPHIA

IT HAS been known for many years that infectious hepatitis may occur in infants and small children.[1] Relatively few cases, however, have been reported, and the incidence of the disease in children under 3 years of age is said to be low.[2] Molner and Meyer,[1e] for example, in reporting on 194 children with the disease from Detroit, found only 5 between the ages of 1 and 4 years, but 77 between the ages of 5 and 9 years. Although this age differential may be due in part to residual maternal immunity or to the lack of exposure, it may also be the result of failure

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From the Department of Medicine, Northwestern University Medical School, and the Liver Research Laboratory of St. Luke's Hospital, Chicago (Dr. Bennett, Dr. Capps, Dr. Ettinger, and Miss Mills), and from the Department of Pediatrics, University of Pennsylvania School of Medicine and the Children's Hospital, Philadelphia (Dr. Drake and Dr. Stokes).

1. (*a*) Cockayne, E. A.: Catarrhal Jaundice, Sporadic or Epidemic: Its Relation to Acute Yellow Atrophy of the Liver, Quart. J. Med. **6**:1, 1912-1913. (*b*) Pickles, W. N.: Epidemic Catarrhal Jaundice: An Outbreak in Yorkshire, Brit. M. J. **1**:944, 1930. (*c*) Findlay, G. M., and Dunlop, J. L.: A Fatal Case of Acute Necrosis of the Liver Associated with Epidemic Catarrhal Jaundice, ibid. **1**:652, 1932. (*d*) Barber, H.: Infective Hepatic Jaundice, ibid. **1**:67, 1937. (*e*) Molner, J. G., and Meyer, K. F.: Jaundice in Detroit, Am. J. Pub. Health **30**:509, 1940. (*f*) Evans, P.: Comments on an Epidemic of Hepatitis, Brit. M. J. **2**:446, 1942. (*g*) Ford, J. C.: Infective Hepatitis, Lancet **1**:675, 1943. (*h*) Cookson, J. S.: Epidemic Infective Hepatitis in Gloucestershire, Brit. M. J. **1**:687, 1944. (*i*) Kunkel, H. G., and Hoagland, C. L.: Observations on a Family Epidemic of Infectious Hepatitis, New England J. Med. **236**:891, 1947. (*j*) Randolph, M., and DeVito, A.: Infectious Hepatitis, Clin. Proc. Child. Hosp. **3**:244, 1947. (*k*) Webb, C. H.; Wolfe, S. G.; Lucas, R. T., and Anderson, C. E., Jr.: Acute Hepatitis in Children: Clinical Features and Laboratory Tests, South. M. J. **40**:340, 1947. (*l*) Fager, D. B.: Infectious and Toxic Hepatitis in Children, Proc. Inst. Med. Chicago **18**:100, 1950.

2. Footnote 1*a*, *e* to *g*, *j*, and *k*.

to recognize the disease. The degree of susceptibility would appear to be fairly high from Cookson's [1h] finding that 20 of 66 children, mostly under 4 years of age, in a children's nursery acquired hepatitis with jaundice.

Adequate descriptions of the clinical and laboratory findings in this age group are not available. The disease is reported to be unusually mild, transitory, and generally without sequelae.[3] Relatively few instances of persistent or recurrent forms [1a] or of fatalities [4] are on record. Although nonicteric cases have been recognized clinically,[5] their frequency is not known. Webb and associates [1k] stated that 9 of 15 children between 1 and 5 years of age with the disease were without jaundice, a figure in accord with the experience of one of us (J. S. Jr.).

Many epidemics of infectious hepatitis involving children have been described, and among them were institutional epidemics in children's hospitals or nurseries [6] and in boarding schools.[7] However, definitive data concerning many of the most important epidemiologic features of the disease have not been obtained. The mode of transmission is still in doubt, many observers favoring an air-borne type of spread,[8] while others favor the fecal-oral route.[9] In adults, experimental evidence clearly indicates that the disease may be produced by the ingestion of infected feces,[10] but evidence of air-borne transmission is equivocal at best.[11] Recently we have been able to show that the virus was not transmitted by the air-borne route in a naturally occurring epidemic.[12] In regard to the question of a carrier state in infants and the

3. (*a*) Footnote 1*f*, *j*, and *k*. (*b*) Horstmann, D. M.; Havens, W. P., Jr., and Deutsch, J.: Infectious Hepatitis in Childhood, J. Pediat. **30**:381, 1947.

4. Footnote 1*c*, *d*, and *l*.

5. (*a*) Footnote 1*f*, *g*, *i*, and *k*. (*b*) Cullinan, E. R.: Epidemiology of Jaundice, Proc. Roy. Soc. Med. **32**:933, 1939.

6. Footnote 1*f* and *h*. Horstmann and others.[3b]

7. (*a*) Footnote 1*b* and *g*. (*b*) Glover, J. A., and Wilson, J.: An Extensive Epidemic of Catarrhal Jaundice, Lancet **1**:722, 1931. (*c*) Lisney, A. A.: Epidemic Catarrhal Jaundice in School Children, Brit. M. J. **1**:703, 1937.

8. Footnote 1*a*, *b*, and *f*. Cullinan.[5b] Glover and Wilson.[7b] Edmonds, H. W.: Recent Advances in Pediatric Pathology: Jaundice in Childhood, West. J. Surg. **54**:50, 1946.

9. Footnote 1*d* and *i*. Lisney.[7c]

10. (*a*) Voegt, H.: Zur Aetiologie der Hepatitis epidemica, München. med. Wchnschr. **89**:76, 1942. (*b*) Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. **12**:139, 1943. (*c*) MacCallum, F. O., and Bradley, W. H.: Transmission of Infective Hepatitis to Human Volunteers, Lancet **2**:228, 1944. (*d*) Havens, W. P., Jr.; Ward, R.; Drill, V. A., and Paul, J. R.: Experimental Production of Hepatitis by Feeding Icterogenic Materials, Proc. Soc. Exper. Biol. & Med. **57**:206, 1944. (*e*) Findlay, G. M.; Martin, N. H., and Mitchell, J. B.: Hepatitis After Yellow Fever Inoculation: Relation to Infective Hepatitis, Lancet **2**:301, 340, and 365, 1944. (*f*) Neefe, J. R.; Stokes, J., Jr., and Reinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Am. J. M. Sc. **210**:29, 1945.

11. Footnote 10*c*. Neefe, J. R., and Stokes, J., Jr.: An Epidemic of Infectious Hepatitis Apparently Due to a Water Borne Agent: Epidemiologic Observations and Transmission Experiments in Human Volunteers, J. A. M. A. **128**:1063, 1945. Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization: Transmission by Intranasal Installation, Lancet **1**:678, 1943. Havens, W. P., Jr.: The Period of Infectivity of Patients with Experimentally Induced Infectious Hepatitis, J. Exper. Med. **83**:251, 1946. Findlay, G. M.: Infective Hepatitis in West Africa, Month. Bull. Min. Health & Pub. Health Lab. Serv. **7**:2, 1948.

12. Capps, R. B.; Bennett, A. M., and Stokes, J., Jr.: Endemic Infectious Hepatitis in an Infants' Orphanage: I. Epidemiologic Studies in Student Nurses, A. M. A. Arch. Int. Med. **89**:6, 1952.

role played by unrecognized acute nonicteric cases in the spread of the disease, practically nothing is known. The former possibility has been suggested,[1a, b] as well as the latter,[1d, f] but with very little supporting evidence.

The principal difficulty encountered in attempting to study infectious hepatitis in infants is that of diagnosis, because specific criteria have not been established. This applies particularly to mild and nonicteric forms. In the absence of a susceptible laboratory animal, only the production of the disease by the administration of infectious material to adult volunteers can be used as definitive proof of the presence of the virus. An almost analogous situation, however, may occur in an epidemic involving both adults and infants if the former can be shown to have contracted the disease from the latter. In a previous paper we have described such an epidemic in an orphanage for infants and small children.[12] Over a period of eight years 73 nurses acquired typical infectious hepatitis, 71 of whom were jaundiced. It was shown conclusively that they contracted the disease from the children and that infection occurred by the fecal-oral route. Convincing clinical and laboratory evidence of liver disease in the children was obtained.[13] Finally, in two children, the presence of virus in the feces was experimentally demonstrated by the

TABLE 1.—*Average Census of Infants and Children by Age and by Floor in 1949*

	Age, Mo.			
	0-6	6-12	12-36	Total
Receiving dept.	34	8	3	45
Newborn nursery	12	..	..	12
Fourth floor	..	..	45	45
Fifth floor	38	30	2	70
Totals	84	38	50	172

use of volunteers.[14] The purpose of this report is to present the epidemiologic aspects of our findings in the children.

DESCRIPTION OF THE ORPHANAGE

As previously described,[12] the orphanage where the epidemic occurred is a five-story building equipped to handle up to 200 infants and children, who are distributed according to age as shown in Table 1. New patients stay in the receiving department for about three weeks, although occasionally their stay is much longer, and are then transferred to either the fourth or the fifth floor. The fifth-floor children are transferred to the fourth floor upon their reaching approximately one year of age. Although the average stay on these two floors is four months, it is quite variable and, in many instances, it is much longer. Infants born in the institution are cared for in the newborn nursery on the second floor. After one to three weeks they are either discharged or transferred to the fifth-floor nursery. No children are kept in the institution after 3 years of age.

13. (*a*) Capps and others.[12] (*b*) Capps, R. B.; Bennett, A. M.; Mills, E. H.; Ettinger, R. H.; Drake, M. E., and Stokes, J., Jr.: The Clinical Picture and Diagnosis of Infectious Hepatitis in Infants and Small Children, to be published.

14. (*a*) Capps and others.[12] (*b*) Stokes, J., Jr.; Drake, M. E., and Capps, R. B.: The Carrier State in Viral Hepatitis, to be published.

Nursing Technique.—Since the orphanage is a well-baby institution, nursing procedures have not been conducted as in a hospital. As previously described in detail,[12] individual isolation is employed only for infants under 6 months of age. The older children are segregated into several wards on each floor and are allowed to play together within these groups. Prior to December, 1949, reasonably aseptic nursing technique was practiced only in the wards for infants under 6 months of age. Among the older children on the fifth floor and in the receiving ward the technique was fair, but on the fourth floor aseptic measures were not really attempted. Since the children are usually not toilet-trained and fecal contamination of clothes and bedding is common, the situation afforded an excellent opportunity for the spread of a fecal-borne infection both from child to child and from child to nurse. In December, 1949, in order to protect the nurses, proper technique was put into effect throughout the institution. Emphasis was placed on hand-washing after handling patients or potentially contaminated objects. This was implemented by the installation of adequate washing facilities.

TABLE 2.—*Total Admissions by Three-Month Periods and by Age; Number of These Children Receiving Liver-Function Tests at Any Time During Their Stay in the Institution*

Interval	Total Admissions	No. by Age, Mo.			Number Tested	No. by Age, Mo.		
		0-6	6-12	12-36		0-6	6-12	12-36
Oct.-Dec., 1949	80	49	5	26	17	4	2	11
Jan.-March, 1950	80	46	11	23	31	10	6	15
April-June, 1950	77 *	30	11	26	39 †	12	8	17
July-Sept., 1950	68	32	6	30	46	22	5	19
Oct.-Dec., 1950	93	56	8	29	47	21	4	22
Jan.-March, 1951	97 ‡	43	12	41	32	0	2	30
April-June, 1951	100	55	8	37	35	4	1	30
Totals	595	317	61	212	247	73	28	144

* Age of four children is unknown.
† Age of two children is unknown.
‡ Age of one child is unknown.

METHODS OF STUDY

Limitation of laboratory facilities, as well as difficulties encountered in repeated bleeding of infants, made it impossible to keep all patients in the institution under observation. Attention was first directed to the fourth-floor children because of the high incidence of hepatitis among the nurses on this floor. For approximately 10 months, beginning in October, 1949, all children on this floor were followed with serial laboratory tests. Subsequently, only specific wards including about half the children on the floor were so studied. Unselected aliquots of children were regularly observed in the receiving ward. The children on the fifth floor, on the other hand, received little attention, although some of the wards were occasionally surveyed. When sick children were discovered either on the fifth floor or in the receiving ward, they were followed in a serial manner.

The actual number of children studied with laboratory tests among the total admitted in each three-month period is shown in Table 2. There were, in addition, more than 60 children present in the institution prior to October, 1949, who were studied serially and others who were studied occasionally. The table also shows that children of all age groups were observed, although the greatest attention was given to children between 1 and 3 years old. About one-half of the children admitted were discharged in less than three weeks.

On serially studied children we made clinical observations, with particular emphasis on symptoms and liver size, on the average of twice a week. Blood was drawn for analysis in the

Liver Research Laboratory of St. Luke's Hospital approximately every two weeks. Liver-function tests routinely employed were the van den Bergh, the thymol-turbidity, the thymol-flocculation, the cephalin-cholesterol-flocculation, the ammonium sulfate turbidity, the scarlet red, the serum alkaline phosphatase, and the choline esterase determinations. Cholesterol esters were occasionally determined. In addition, the urine was analyzed for urobilinogen, coproporphyrin, and bilirubin. The technical procedures have been described elsewhere.[13]

In April, 1950, extensive skin testing was first performed, using the amniotic material of Henle and co-workers.[15] Readings were made at 24 and 48 hours. The first tests were read by two of us (M. E. D. and J. S. Jr.) who were unaware of the clinical diagnosis in each case. Subsequent tests were read by others.

Diagnostic Criteria.—The diagnostic criteria employed were necessarily arbitrary. Since the clinical picture of infectious hepatitis in this age group is relatively nonspecific, the diagnosis was based largely on laboratory findings. A detailed analysis of these data, along with those obtained from normal control children and children with other infections, will be presented in a subsequent report.[13b] Suffice it to say that, for the purposes of this paper, only those children who had at least three different tests with clearly positive reactions for four weeks or longer were accepted as having infectious hepatitis. In most cases lassitude, gastrointestinal disturbances, and hepatomegaly were also present. Borderline cases were classified as "probable." It was recognized that many cases were undoubtedly excluded from consideration by these arbitrary criteria. This includes cases with insufficient data, especially those in which testing was begun too late. Nevertheless, it appeared best to err on the conservative side. The validity of our diagnoses was confirmed, as will be subsequently described, by the results of skin testing, as well as by the demonstration of virus in the feces in two cases in experiments with adult volunteers. Other infections known to be associated with liver injury, particularly infectious mononucleosis and amebiasis, were ruled out.

The date of onset of illness was based on the onset of symptoms coinciding with or preceding the first positive liver-function test. This was necessary because in many instances there was a two- to four-week interval between the last normal control set of test reactions and the first abnormal reactions. Although the onset was in most cases reasonably clear, in some it was less definite and in the "probable" cases it was difficult to determine.

GENERAL DESCRIPTION OF THE EPIDEMIC

The children presumably became infected with the virus in 1942, when the first cases of infectious hepatitis in nurses were reported.[12] Since the children were still infected at the time of this report, June, 1951, the epidemic has been in progress for about 10 years. This report covers our observations over the last 22 months. No specific data concerning the children are available for the prior period.

During the initial three months of observation, neither the customary segregation of the children in different wards and on separate floors nor the institutional routine was disturbed in any way. In December, 1949, nursing technique was revised as previously described. On Jan. 15, 1950, when it had become apparent that infectious hepatitis was endemic among the children, isolation measures were instituted. Separate isolation wards were set up for all children known to have

15. (*a*) Henle, G.; Drake, M. E.; Henle, W., and Stokes, J., Jr.: Skin Test for Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **73**:603, 1950. (*b*) Henle, W.; Harris, S.; Henle, G.; Harris, T. N.; Drake, M. E.; Mangold, F., and Stokes, J., Jr.: Studies on the Agent of Infectious Hepatitis: I. Propagation of the Agent in Tissue Culture and in the Embryonated Hen's Egg, J. Exper. Med. **92**:271, 1950. (*c*) Drake, M. E.; Kitts, A. W.; Blanchard, M. C.; Farquar, J. D.; Stokes, J., Jr., and Henle, W.: Studies on the Agent of Infectious Hepatitis: II. The Disease Produced in Human Volunteers by the Agent Cultivated in Tissue Culture or Embryonated Hen's Eggs, ibid. **92**:283, 1950.

the active disease and for all those who had recovered from the disease. Unfortunately, this attempt to prevent further spread proved unsuccessful and after seven months was discarded, in August, 1950, in favor of other measures.

During this 22-month period, infectious hepatitis was diagnosed in 42 infants and children (Fig. 1). The condition of six of these was classified as borderline ("probable"), and so they have been omitted from certain of our data as indicated. Eleven of these 42 children were less than 1 year of age and 4 were under 6 months. Fifteen were sick for more than three months and three for more than six months. In only one child was jaundice or hyperbilirubinemia observed.

The distribution of cases throughout the study period is shown in Figure 1. The incidence of new cases was not materially altered by the change in nursing technique, the isolation of children known to have the active disease, or the discontinu-

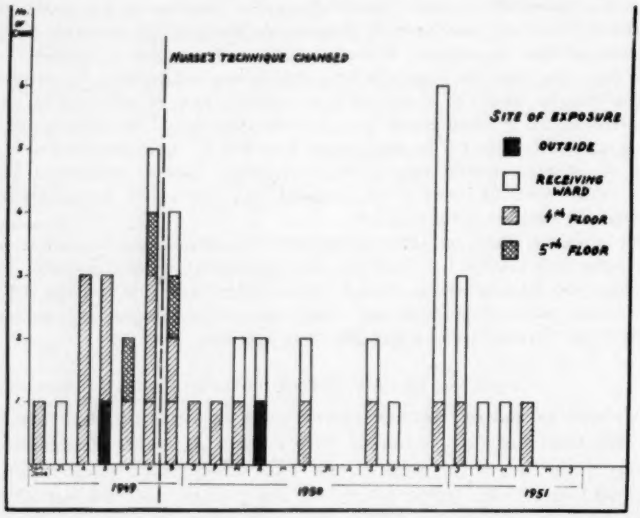

Fig. 1.—Monthly incidence of new cases of infectious hepatitis in infants and children. Note essentially continuous nature of epidemic.

ance of such isolation measures. This becomes more evident if the fourth-floor cases are considered alone. Only on this floor were observations reasonably continuous and inclusive of all children.

Incubation Period.—In order to determine the probable site of infection it was necessary to establish the incubation period. In Table 3 is shown the elapsed time between admission to the institution and onset of illness. The probable cases have been omitted, since the date of onset in these children was somewhat uncertain. It will be seen that 8 of the 36 children became ill in 11 to 14 days. If these eight all contracted the disease on the outside, then they must all have been infected approximately the same number of days before admission. It seems highly improbable that this would be true of almost 25% of the total number affected. Further-

more, these eight were not admitted as a group but at widely scattered intervals. It must, therefore, be concluded that these children became infected shortly after entering the receiving ward and that 11 or 12 days represents the minimum incubation period. Although in adults 16 or more days is usually taken as the minimum incubation period, the period is frequently calculated from the onset of jaundice or the onset of positive laboratory findings instead of from the onset of symptoms. The latter may precede the former by three or four days or more. We have personally observed clear-cut 12-day incubation periods from exposure to onset of symptoms in adults. In the volunteers who were infected with this particular strain of virus,[14b] the onset of jaundice occurred 23 and 24 days after exposure, respectively. Allowing for a prodromal preicteric period of 7 to 10 days, this would give an incubation period not inconsistent with that of the children.

TABLE 3.—*Incidence of Short Incubation Periods* *

	Type of Onset			Type of Onset	
	Definite	Less Definite		Definite	Less Definite
Days	No. of Cases		Days	No. of Cases	
0	1	..	20	1	..
11	2	2	21	..	1
12	1	1	22-28	1	..
14	1	1	29-35	..	3
19	1	..	36 plus	6	14

* Interval in days from admission to institution to onset of hepatitis in 36 definite cases of the disease in infants and small children.

TABLE 4.—*Site of Infection in Forty-Two Infants and Small Children with Infectious Hepatitis*

	No. of Cases
Outside institution	2
Receiving department	17
5th floor	3
4th floor	20

Site of Origin.—Based on the above minimum incubation period, the site of infection for all 42 infants and children has been determined as shown in Table 4 and Figure 1. It will be noted that two children were sick on admission. It will also be seen that new cases of the disease developed on all floors of the institution with children's wards. The small number of cases observed on the fifth floor was due in part and perhaps entirely to the limited studies made on this floor.

EPIDEMIC SPREAD

Results of serial studies on all children in two separate wards are shown in Figures 2 and 3. Each horizontal bar represents a child, the left end indicating the date of admission to the ward. Inspection of Figure 2 shows that Child 3 was apparently the initial source of infection. She had been sick since April 1 with symptoms identical to those manifested in September. Although several of the other children who had been in the ward for some months were reported to have had prior symptoms suggestive of hepatitis, only this one had positive findings during

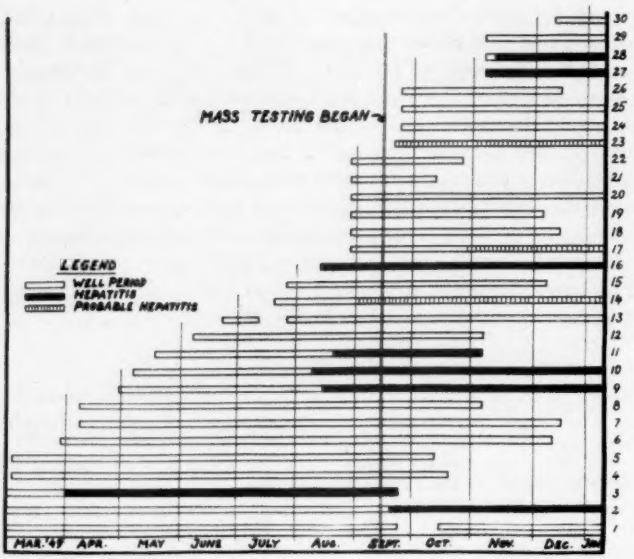

Fig. 2.—Spread of infectious hepatitis in Ward 4*S*. Graph shows all children in ward between Sept. 15, 1949, and Jan. 10, 1950.

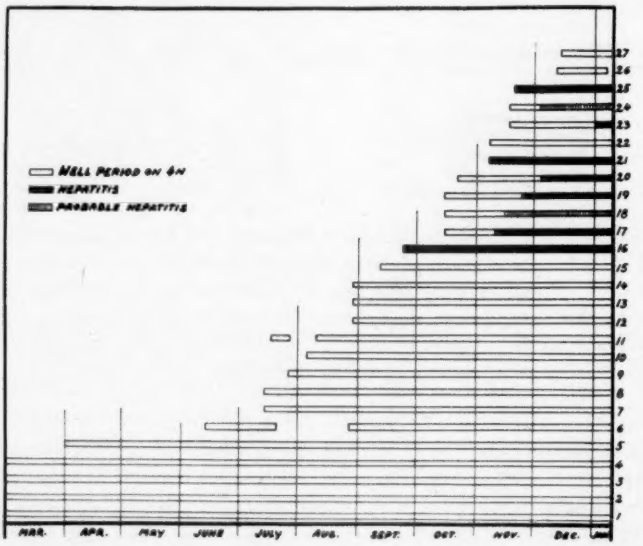

Fig. 3.—Spread of infectious hepatitis in Ward 4*N*. Graph shows all children in ward during study period, Dec. 1, 1949, to Jan. 10, 1950. Testing began Dec. 1, 1949. Child 16 is same as Child 3 in Figure 2, and Child 21 is same as Child 11.

our period of observation. She was apparently responsible for the disease in Children 9, 10, and 11. Patients 16, 23, and 27 were obviously sick on admission. The remaining children appear to have been secondary contacts. In addition to the children, two nurses acquired hepatitis, one on Sept. 21 without jaundice and one on Nov. 12 with jaundice. They also were probably secondary contacts.

In Figure 3 is shown the situation in Ward 4*N*. Here children present in the group prior to September, 1949, were reported as having been well. On Sept. 24, 1949, Child 3 from Ward 4*S* was accidentally transferred to Ward 4*N*, where she is indicated as Child 16, and the resulting outbreak is obvious. She is the only apparent source of infection for patients 17 and 18. Children 19, 20, 23, and 24 were apparently secondary contacts, and Children 21 and 25 were ill on admission to the ward. In addition to the children, seven nurses in the ward contracted hepatitis, six with jaundice. The first three nurses showed the disease on Oct. 28, Nov. 1, and Nov. 11, respectively. They apparently were infected by Child 16.

These two graphs indicate the manner in which the infection spread. It was not explosive. The epidemic pattern, as well as the appearance of the disease in nurses,

TABLE 5.—*Results of Skin Tests with Irradiated Virus Done in April, 1950*

	Number Tested	Number Positive	Per Cent Positive
Nurses			
History of icteric hepatitis	14	13	92.8
History of nonicteric hepatitis	3	3	100.0
No history of hepatitis	28	10	34.3
Children			
With clinical hepatitis	15	13	86.3
Without clinical hepatitis	67	33	49.2
In receiving ward	28	3	10.7

strongly supports our diagnosis for the children. The diagnosis is further substantiated by the fact that Child 11 (Fig. 2), who was transferred on Nov. 7, 1949, to Ward 4*N*, where she is Child 21 (Fig. 3), was found in an experiment with volunteers to have virus in a stool specimen obtained on Jan. 27, 1950.[14b] It will be noted that those whose disease was acquired in the ward, the secondary contacts, were children who had only recently been admitted to the group. They were mostly transfers from the receiving department. This presumably indicates that the older members of the group were immune because of previous infection.

RESULTS OF SKIN TESTS

In Table 5 are seen the results of a skin-test survey done in 1950. For comparison the results in nurses are shown at the top. The figure of 34.3% positive tests in nurses without a history of infectious hepatitis is similar to the usual incidence of positive tests in unselected groups of young adults.[15a] It apparently indicates the incidence of immunity from unrecognized prior infection. The excellent correlation with the clinical diagnosis is obvious. The results in the children are equally convincing, and both confirm our clinical diagnosis, as well as the validity of the skin test. The two children with clinical hepatitis who had negative skin tests had the chronic disease. One of them was subsequently retested one year later,

and the reaction was found to be positive. A question might be raised regarding the significance of the second figure, 49.2%. That this indicates previously unrecognized infection and not false-positive tests is shown by a comparison with the

TABLE 6.—*Relation of Skin Test to Duration of Disease in Infants and Small Children with Clinical Infectious Hepatitis*

		Positive Skin Test		Negative Skin Test	
Wk. from Onset to Skin Test	Total Tested	No. of Cases	No. with Positive Liver-Function Tests	No. of Cases	No. with Positive Liver-Function Tests
0-1	1	0	..	1	1
1-2	1	0	..	1	1
2-3	1	1	1	0	..
3-4	0	..	..	..	..
4-8	1	1	1	0	..
8-12	2	1	1	1	1
12-16	4	2	1	2	2
16-20	6	5	3	1	1
20-24	4	3	2	1	1
24-52	9	5	2	4	4
53-72	2	2	1	0	..
Total	31	20	12	11	11

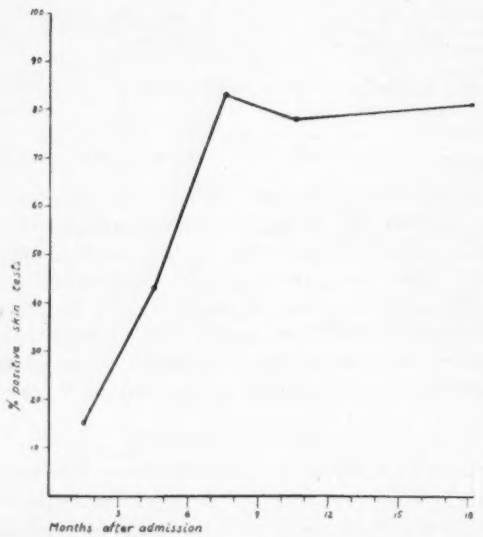

Fig. 4.—Incidence of positive skin tests in relation to the duration of exposure in the institution. Graph shows that peak of 80% was reached after a stay of six months.

figures for the receiving ward. The latter children had not yet been exposed to the institutional epidemic.

A further analysis of all skin tests in children with a clinical diagnosis of the disease, including patients skin-tested subsequent to April, 1950, is shown in Table 6.

Although only 65% of the reactions were positive, it will be noted that all skin-test-negative children had laboratory evidence of active hepatitis at the time of the test. In comparison, only 60% of skin-test-positive children had laboratory evidence of activity of the disease. If the children with active hepatitis are considered as a group, approximately 50% had positive and 50% had negative skin tests. In conjunction with the previously mentioned child having the chronic disease in whom the skin test changed from negative to positive at the time of clinical convalescence, the data suggest that persistent clinical activity is often associated with lack of immunity as indicated by the skin test. It should also be noted in Table 6 that the child who exhibited a positive test earliest was in the third week of the disease. Two children not included in the table were tested six weeks or more prior to the onset of the

TABLE 7.—*Relation Between Length of Hospital Stay and Percentage of Positive Skin Tests*

Mo. After Admission	Total Tested	Positive Skin Tests	Percentage Positive
0-1	14	2	14
1-2	7	1	14
2-3	6	1	17
3-4	5	1	20
4-5	7	4	57
5-6	9	4	44
6-7	9	7	78
7-8	1	1	100
8-9	2	2	100
9-10	6	5	83
10-11	2	1	50
11-12	1	1	100
12 plus	21	17	81
Totals	90	47	Average, 52

TABLE 8.—*Incidence of Positive Skin Tests by Floors* *

Floor	Total Tested	No. Positive	Per Cent Positive
5th	19	17	89.5
4th	21	15	71.4
Receiving	28	3	10.7

* Only those children are included in fourth-floor group who were never on fifth floor.

disease, one with a positive reaction and the other with a negative result. The child with the positive reaction was subsequently tested 20 weeks after onset of illness, and data on this test are shown in the table. At this time her test was negative, and she still had persistent laboratory evidence of activity. No satisfactory explanation is available for the first positive reaction in this child. It should also be pointed out that the children with hepatitis shown in Table 5 had mostly old cases at the time of skin testing, probably explaining the high percentage of positive results in that group.

INCIDENCE

The total over-all incidence of infection is best shown by the results of the skin test. In Table 7 the patients have been divided according to the duration of their exposure, as indicated by the hospital stay, and the percentage of positive skin tests determined for each group. These data are depicted graphically in Figure 4,

using averages for three-month periods. It is clear that the incidence of positive tests rises sharply during the fourth month and after six months reaches a figure of approximately 80%. This is very convincing evidence that most of the children were ultimately infected. In Table 8 are shown the data arranged according to floors. This table indicates that infectious hepatitis was prevalent on the fifth as well as on the fourth floor.

Clinically Diagnosed Cases.—The incidence of clinically diagnosed cases is shown in Table 9. Only those children actually admitted during the study period who remained in the institution for three weeks or more have been analyzed. This group was chosen because hepatitis without jaundice cannot be contracted and diagnosed in less than three weeks. It will be noted that in 26 children of 188 receiving laboratory tests the diagnosis of hepatitis was made, an incidence of about

TABLE 9.—*Children Remaining in Institution Three Weeks or More After Admission, Number Receiving Liver-Function Tests, and Incidence of Hepatitis in the Latter*

Interval	Total	No. Tested	No. Exhibiting Hepatitis Within			Total
			2 Wk.	2-4 Wk.	4 Wk.+	
Oct.-Dec., 1949	42	16	1	..	6	7
Jan.-March, 1950	48	20	2	1	..	3
April-June, 1950	57	31	1	..	3	4
July-Sept., 1950	52	40	..	..	2	2
Oct.-Dec., 1950	61	40	1	3	3	7
Jan.-March, 1951	55	18	2	1	..	3
April-June, 1951	52	23	..	..	..	..
Totals	367	188	7	5	14	26

TABLE 10.—*Incidence of Hepatitis in Well Children Transferred to and Exposed on Fourth Floor; Comparison of Those from Receiving Department with Those from Fifth Floor*

From	Total	No. Contracting Hepatitis	Per Cent of Total
5th floor	21	3	14
Receiving department	22	10	45

14%. Since only about 100 of the 188 patients tested were observed repeatedly and some of these were not studied continually from time of admission to discharge, it is clear that this incidence is unduly low. It confirms the validity of our diagnostic criteria, although indicating that they are probably too rigid. However, based on the skin-test data shown in Figure 4, it is estimated that 50 to 80% of these 188 patients actually became infected, as their average stay was about seven months. It follows that there must have been a high incidence of inapparent cases, possibly in the neighborhood of 50% of the total cases.

Table 9 also shows the number of cases of hepatitis developing within a short time after admission. Seven of the 26 children displayed the disease within 11 to 14 days and, therefore, must have been infected during their first few days in the institution. Twelve of the 26, or almost 50%, exhibited the disease within four weeks after admission and therefore must have been infected during the first two weeks of their stay. This indicates that infectious hepatitis was highly contagious under the existing conditions.

Immune Children.—The above conclusions regarding total over-all incidence are substantiated by evidence of immunity. Thus, it is clear from Figures 2 and 3 that only the newly admitted children were susceptible to the infection. Apparently those in the institution longer were immune. In Table 10 is shown the incidence of infection in patients transferred to the fourth floor. Those from the receiving ward were largely susceptible, although they were followed for an average of only 30 days, whereas those from the fifth floor were mostly immune, although they were followed for an average of three months. In addition, of seven children transferred from Ward 4*S* to Ward 4*N*, none acquired hepatitis. These data provide clinical evidence that there was a high incidence of immune children among those who had been exposed in this institution for a period of months.

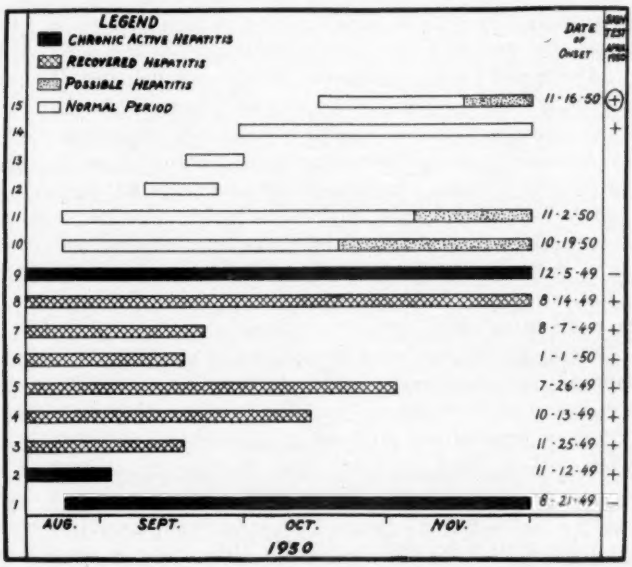

Fig. 5.—Infectious hepatitis in an isolated group of children. Children 10, 11, and 15 were apparently infected by either Child 1 or Child 9, providing epidemiologic evidence of a prolonged fecal carrier state.

EVIDENCE OF CARRIERS

Strong epidemiologic evidence of a carrier state has been presented in Figures 2 and 3. Child 3 in Figure 2 was apparently the source of infection for at least three children in Ward 4*S*. When transferred to Ward 4*N* (Fig. 3), where she is indicated as Child 16, she again apparently started a subepidemic, being directly responsible for two cases in children and three in nurses. Since the onset of her illness was approximately April 1, it appears that she had remained contagious for seven months. Two other groups were observed later in which the responsible children had been ill for four months and one year, respectively. In neither case, however, was the evidence as strong as in this one.

In Figure 5 is shown another and very suggestive group. Children 1, 2, and 9 had the chronic disease which was still clinically active, that is, with abnormal liver-function tests and symptoms. Children 3 to 8, inclusive, were clinically recovered. It will be noted that the most recently ill child of the group was Child 9, who had her onset on Dec. 5, 1949. Six normal children were admitted to the ward. Two of these, Children 12 and 13, were discharged shortly. One, Child 14, remained well but, since she had had a positive skin test in April, was probably immune at the time of admission. The other three children, 10, 11, and 15, displayed symptoms typical of infectious hepatitis. Laboratory findings were very suggestive, but not sufficiently striking to satisfy our diagnostic criteria. Consequently, these have been classified as "possible" cases. The fact that all three children were involved, however, increases the likelihood that they did, in fact, have infectious hepatitis. In addition, Child 15 had a positive skin test in April, 1951. If this is true, then they must have become infected in October, 1950. At this time Child 9 had been sick for more than nine months, and the other children, representing a potential source of infection, for an even longer period.

Although several groups were studied in which new susceptible children were exposed to clinically recovered children, no epidemiologic evidence of a carrier state in the former was obtained. In addition, approximately 300 parents and foster parents who were taking care of children discharged from the orphanage were questioned. Children known to have infectious hepatitis were not allowed to be taken out of the institution except in unusual circumstances. No evidence was obtained that infectious hepatitis developed in any parents, foster parents, or other members of the households.

The significance of Figure 5 and the existence of a fecal carrier state have now been confirmed by feeding fecal material obtained from two of these children to separate groups of adult volunteers. As will be subsequently described in detail,[14b] typical infectious hepatitis was produced in each instance. Child 9 (Fig. 5) had virus in her stool on March 17, 1951. Since the onset of her illness was Dec. 5, 1949, this indicates that virus was present in the stool more than 15 months after onset. Child 1 in Figure 5, who is the same as Child 11 in Figure 2 and Child 21 in Figure 3, had virus in her stool on Jan. 27, 1950. Since the onset of her illness was Aug. 21, 1949, she had been a carrier for nearly five months.

INFANTILE DIARRHEA

In April, 1950, an epidemic of so-called infantile diarrhea broke out in the institution. As is so often the case, stool cultures and other attempts to determine the etiology were unsuccessful. Fourteen of these infants were skin-tested two to three weeks after onset, and in 12 instances the reactions were positive. Unfortunately, laboratory procedures were not carried out, nor had skin tests been done prior to illness. Eleven of these 13 infants were 2 weeks to 4 months of age. The other three were 12, 9, and 8 months old, respectively. Although it is possible that acquired immunity from the mother may produce a positive skin test in newborn infants, 17 unselected infants under 6 months of age who were tested on admission all had negative reactions. This is suggestive evidence that the syndrome of infantile diarrhea may on occasion be produced by the virus of infectious hepatitis.

COMMENT

The epidemiologic studies reported here and previously [12] have conclusively demonstrated that infectious hepatitis was endemic among the infants and small children in this institution. A question might be raised as to which children actually had the disease. The validity of our clinical and laboratory diagnostic criteria is confirmed by the demonstration of an epidemic pattern particularly impressive on Wards 4*S* and 4*N*, where nurses were simultaneously involved, by the excellent correlation of skin-test results with the clinical and laboratory findings, and finally by the demonstration of virus in the feces of the only two children tested. The chief fault with these criteria appears to be that they were too strict and caused the elimination of too many actual cases. Perhaps further studies will provide better diagnostic procedures.

The Skin Test.—The introduction of a specific method for determining immunity in this disease has considerable significance in the present studies. The correlation between the results of the skin test and the clinical and laboratory findings strongly supports the validity of the former and provides valuable epidemiologic data as well. The suggestive evidence obtained that chronic hepatitis is associated with an absence of immunity is a matter of considerable interest.

Incidence and Susceptibility.—It is clear both from the skin-test and the epidemiologic data, as well as from the clinical and laboratory findings, that the over-all incidence of the disease was very high, probably about 80% in those exposed for six months or more. The infection was present on all floors and in all wards of the institution with the exception of the newborn nursery. In addition, children of all age groups from a few months to 3 years old were involved. The fact that 8 of the 42 children in whom hepatitis was clinically diagnosed contracted the disease almost immediately after entering the receiving ward is an indication of its contagiousness.

The Carrier State.—Perhaps the most important single observation made in this study concerns the carrier state. Epidemiologic evidence was obtained that certain children continued to be contagious over a period of months. Based on these observations, fecal material was obtained and fed to volunteers with positive results. This is the first time that the virus has been experimentally demonstrated to persist for more than two weeks after onset of illness. It is important to note that the disease in both these children was an example of so-called chronic active hepatitis with persistent symptoms, as well as positive laboratory findings. Thus, they did not represent true carriers in the strict sense of the term. No epidemiologic evidence of a true carrier state in clinically recovered children was obtained.

Spread of the Disease.—On the basis of our observations it is impossible to determine the mode of spread with certainty, although parenteral mechanisms were eliminated.[12] Since transmission from child to nurse was clearly through some form of contact, it appears likely that a similar mechanism was involved in the spread from child to child. The absence of explosive outbreaks argues strongly against air-borne transmission. It is unlikely that the nurses were serving as intermediaries, because none of them have had hepatitis since the change in technique in December, 1949. Although direct contact among the children is probably the most important factor, this does not explain cases of the disease among the

smaller infants who are isolated. Four cases occurred in this age group, all in 1950 and 1951. However, this age group was not studied in 1949. Possibly toys and other objects may provide a mechanism for indirect contact.

It is important to point out the role played by the nonicteric cases in this epidemic. Only 1 child of the 42 who received the clinical diagnosis of infectious hepatitis had hyperbilirubinemia. Actually the incidence of jaundice must have been well under 1% if we assume that 50 to 80% of the children became infected. Evidence was obtained that in some of these children, perhaps as many as half of the total, the disease was truly subclinical without diagnostic laboratory evidence of liver dysfunction, but the exact incidence of this form of the disease could not be determined. This is, we believe, the first epidemic on record involving almost entirely nonicteric cases. This demonstrates clearly the importance of the unrecognized nonicteric case in maintaining an epidemic, as we have previously pointed out.[16]

Necessary Factors Responsible for Epidemic.—This epidemic has now persisted for almost 10 years among the children. The factors that have made this possible are a high degree of susceptibility in this age group, frequent fecal contamination, an adequate length of stay of the patients, and the regular introduction into the group of new susceptible children. Another most important factor was the absence of jaundice, which allowed the epidemic to continue for so long a time without being recognized among the children. Finally, the unsuspected presence of fecal carriers and the occasional introduction of new cases from the outside helped to maintain the epidemic. Most of these factors may well be present in other similar institutions or groups and possibly even in children's wards in general hospitals. Obviously, the disease will not be diagnosed if it is not suspected.

Epidemic Control.—It is clear from Figure 1 that the spread of the disease among the children was not influenced by the change in nursing technique or the isolation of potentially contagious children. The reason for this failure lies in the difficulty in establishing the diagnosis early in the disease. The patient has frequently been sick and probably contagious for one or more weeks before the diagnosis is suspected. Whether it is possible to diagnose the disease in all cases on the basis of laboratory findings is not settled, although possibly it can be accomplished in the majority of instances. Finally, our findings of persistent virus in the stool of two patients raises a serious question of the normal duration of virus in the stool. Possibly the virus persists in the stool of many or most patients who run a prolonged course.

It is possible that complete and effective isolation of every infant and child would eventually bring an end to this epidemic. Not only, however, is this entirely impractical, but, in view of the occasional patients admitted with the disease, it would not prevent a recurrence of the epidemic. Some form of active immunization appears necessary in order to effect permanent control.[17]

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16. Capps and others.[12] Capps, R. B.; Sborov, V., and Scheiffley, C. S.: A Syringe-Transmitted Epidemic of Infectious Hepatitis, J. A. M. A. **136**:819, 1948.

17. Capps, R. B., and Stokes, J., Jr.: The Epidemiology of Infectious Hepatitis and the Problems of Prevention and Control, J. A. M. A. **149**:557, 1952.

CONCLUSIONS

An institutional epidemic of infectious hepatitis involving children under 3 years of age is described which has lasted for more than 10 years.

Forty-two cases were recognized clinically, in only one of which was hyperbilirubinemia observed. Epidemiologic evidence indicated that 80% of the children were eventually infected. The epidemiologic importance of the nonicteric case is demonstrated.

The incubation period was found to be as short as 11 days from time of exposure to onset of symptoms.

Suggestive epidemiologic evidence of a fecal carrier state lasting four months to one year after onset of illness was obtained. This was confirmed by the demonstration of the virus in experiments with volunteers in two cases, one of five months' and one of fifteen months' duration.

The necessary conditions for such an epidemic are described. It is pointed out that similar conditions undoubtedly exist elsewhere and are probably unrecognized.

The epidemic has not been controlled in the children, but only in the nurses, by changing nursing technique, nor has the isolation of children known to have the active disease been effective.

ESSENTIAL THROMBOPHILIA

RAYMOND W. MONTO, M.D.
WALTER D. GRIEST, M.D.
AND
D. EMERICK SZILAGYI, M.D.
DETROIT

NYGAARD and Brown [1] in 1937 reported five cases of vascular disease characterized by recurrent episodes of acute occlusions in the large and small arteries of the extremities, heart, kidney, and brain. The findings did not conform to those of the well-known groups of vascular syndromes. It was reported that the occlusive attacks were commonly preceded by localized or migrating thromboses of the superficial or deep veins. The symptoms were directly related to the vascular occlusions, and gangrene of the extremities was frequently observed. Histologic study of the affected vessels indicated a slight cellular reaction in the walls of the vessels and the absence of degenerative or inflammatory vascular disease. Four of the patients studied showed evidence of increased coagulability of the blood during thrombotic episodes. In two patients, elevation of the blood globulins and fibrinogen was observed. This finding was interpreted to be of importance in reducing the suspension stability of the usually increased blood thrombocytes (platelets). For the disease in this group of patients, Nygaard and Brown initiated the name "essential thrombophilia."

Epstein and Richter [2] in 1948 described a sixth case which, in their opinion, fulfilled the criteria of essential thrombophilia. Their patient presented the clinical picture of gangrene of the extremities, as well as symptoms consistent with a pulmonary infarct. Autopsy demonstrated thromboses of the major vessels of the right lower extremity, as well as of the vessels of the spleen and pancreas. Microscopic sections showed but minimal tissue reaction in the vessel walls.

The case here presented exhibited the usual clinical manifestations of essential thrombophilia and demonstrated refractivity to anticoagulants in that coagulation times were not prolonged on heparin therapy. Antemortem bone marrow and blood coagulation studies were made. The autopsy observations are presented.

REPORT OF A CASE

History.—B. W. (H. F. H. 454105), a 65-year-old white retired salesman of Swiss ancestry, fell from a ladder, landed in a sitting position, and immediately suffered excruciating pain in the region of the first lumbar vertebra. The day after his accident a hyperextension body cast

From the Hematology Clinic, Department of Laboratories, and Division of General Surgery, The Henry Ford Hospital.

1. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia: Report of 5 Cases, Arch. Int. Med. **59**:82-106 (Jan.) 1937.

2. Epstein, J. A., and Richter, I. H.: Essential Thrombophilia: Report of a Case, Ann. Int. Med. **29**:545-549 (Sept.) 1948.

was applied by his local physician. Two days later pain and numbness developed, and he noted blanching of the dorsum of the right foot. The signs and symptoms progressed, and he was admitted to the Henry Ford Hospital on Oct. 17, 1949, for further care.

On examination the temperature, pulse rate, and respirations were normal. The right foot was cold and painful to touch, and there was a bluish discoloration extending from the toes to the midportion of the foot. The posterior tibial artery pulsations were easily palpable, but the pulsation of the dorsalis pedis artery was diminished bilaterally. Results of a neurological examination were normal. The remainder of the physical examination revealed an essentially normal condition.

Initial laboratory data showed a hemoglobin concentration of 12.7 gm., 4,510,000 red blood cells, and 38,900 white blood cells, with 90% polymorphonuclear cells in the differential count. The nonprotein nitrogen was 42 mg. and the fasting blood sugar 129 mg. per 100 cc. The prothrombin time was normal. Urinalysis showed a 1+ reaction for albumin, with 6 to 8 granular casts per high-power field in the centrifuged sediment. Roentgenograms of the lumbar spine demonstrated a marked degree of compression of the body of the first lumbar vertebra.

The pertinent findings during the clinical course of the patient are illustrated in Figure 1. He was given a trial of continuous caudal anesthesia for 48 hours, without clinical improvement. Circulatory inadequacy of the right leg from the knee distally was demonstrated by the fluorescein wheal test (Fig. 2). On the fourth hospital day the patient had a sudden severe pain in the left chest. The blood pressure dropped from 145 to 105 mm. Hg systolic and from 88 to 70 mm. Hg diastolic. A clinical diagnosis of pulmonary infarction was made, and anticoagulant therapy was started. Despite continued doses of 400 to 500 mg. of heparin intravenously daily, the patient's coagulation time (Lee-White method) remained at levels of 6 to 10 minutes. On the fourth day of heparin therapy a hematoma developed, involving the left shoulder and arm and necessitating the discontinuance of anticoagulant therapy. By the 10th hospital day the right foot had progressed to the state of dry gangrene, with a line of demarcation at the mid-dorsum of the foot (Fig. 3).

It was noted early in the hospitalization that the patient's blood would congeal soon after it was drawn into the syringe. The coagulation time on the 10th hospital day was eight minutes; the bleeding time was four and a half minutes (Duke method); the reaction to the tourniquet test was negative, and the clot retraction was normal. The thrombocyte count was 906,000 (normal range for the method used, 200,000 to 300,000); fibrinogen was 0.56 gm.; albumin, 3.07 gm., and globulin, 3.46 gm., per 100 cc. The peripheral blood smear showed massed thrombocytes, many of which were giant forms (Fig. 4). The differential count[3] showed 2% myelocytes, 7% metamyelocytes, 65% polymorphonuclear cells, 4% lymphocytes, and 22% monocytes, with a total white blood cell count of 42,500. The blood cold agglutinins were reported as 2+; warm agglutination was negative. A test for the presence of cryoglobulins gave negative results. Repeated blood cultures were negative for pathogens. A sternal marrow aspiration was performed, and the smears revealed the following differential count for 500 cells: 0.6% myeloblasts, 1.0% progranulocytes, 0.6% early neutrophilic myelocytes, 16.0% late neutrophilic myelocytes, 8.0% metamyelocytes, 22% band cells; 19.6% segmented neutrophiles, 2.2% giant neutrophilic metamyelocytes, 0.6% immature eosinophiles, 0.8% eosinophiles, 5.2% lymphocytes, 4.0% monocytes, 0.8% plasmacytes, 0.8% pronormoblasts, 0.6% basophilic normoblasts, 18.0% polychromatophilic normoblasts, 0.6% orthochromatic normoblasts, and 0.4% mitoses. The myeloid-erythroid ratio was 4:1. The marrow smears contained more than the customary number of cells. Large numbers of thrombocytes were frequently observed. Some of the thrombocytes were larger than normal. Bizarre, giant neutrophilic metamyelocytes were not infrequent. The megakaryocytes appeared to be present in normal numbers at this site. However, they at times were toxic and at other times possessed excessively large cell bodies with failure of cytoplasmic azurophilic granular aggregation. Some megakaryocytic nuclei presented pronounced nuclear hyperlobulation to an extent beyond that we had previously seen (Fig. 5). A differential count of 50 marrow megakaryocytes revealed the following distribution: 4% megakaryoblasts, 8% promegakaryocytes, and 88% megakaryocytes. During the survey of the megakaryocytes, the following cytologic features were observed (some cells possessed more than one abnormality):

3. Peripheral blood smear and bone marrow examination were performed by John W. Rebuck, M.D., Department of Laboratories, Henry Ford Hospital.

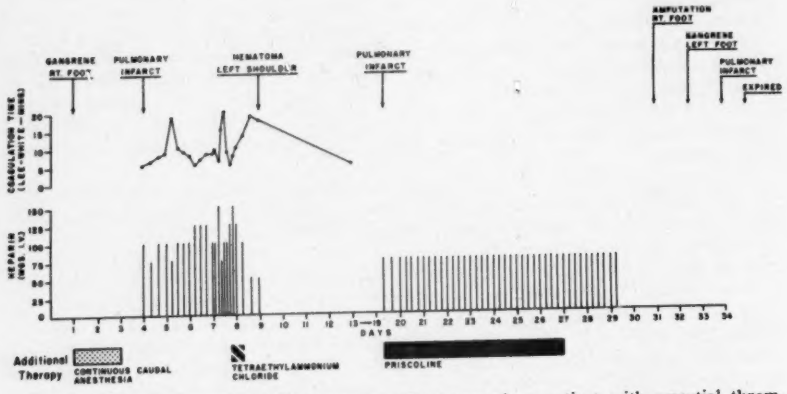

Fig. 1.—Chart illustrating clinical course and treatment in a patient with essential thrombophilia. Priscoline® is 2-benzyl-4,5-imidazoline hydrochloride.

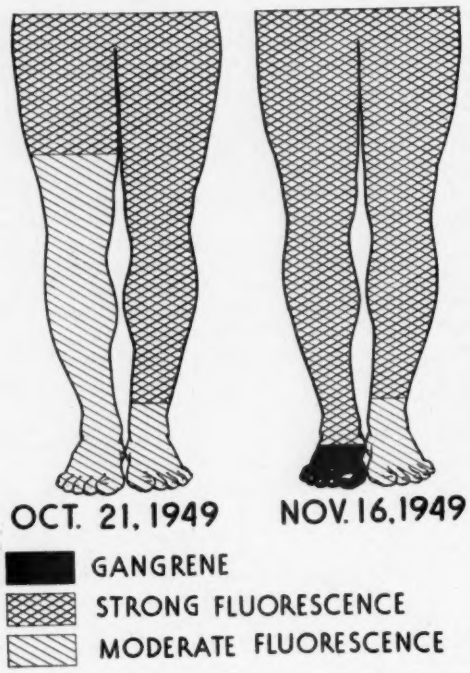

Fig. 2.—Results of histamine-fluorescein wheal test, depicting circulatory inadequacy in a patient with essential thrombophilia.

Fig. 3.—Gangrenous right foot of patient with essential thrombophilia.

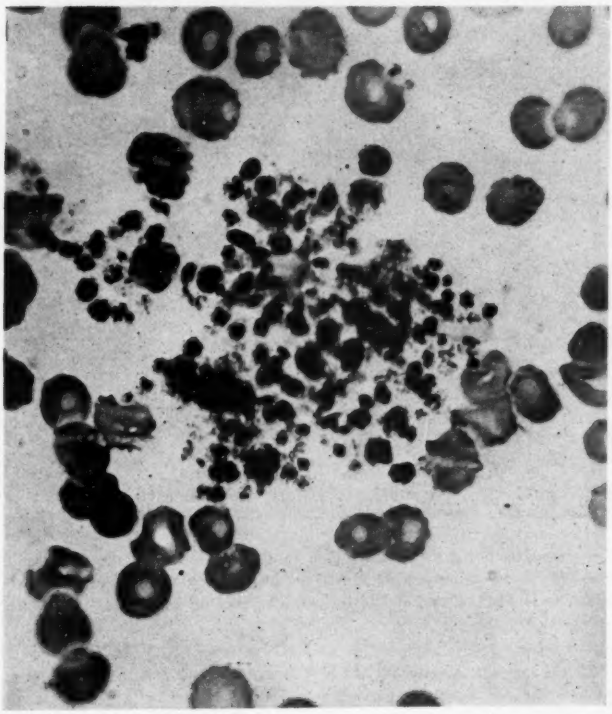

Fig. 4.—Peripheral blood smear, showing large and bizarre-shaped thrombocyte masses in a patient with essential thrombophilia; × 1,200.

unusually large cell bodies, 12; failure of granular aggregation, 22; excessive multilobulation of nucleus, 6; failure of granular formation, 8; degenerated forms, 19; precocious thrombocyte formation, 1, and mitosis, 1.

The clinical picture suggested the diagnosis of essential thrombophilia to one of us (R. W. M.). On the 18th hospital day the patient again experienced an episode typical of pulmonary infarction. Again heparin therapy, 75 mg. every six hours, was instituted and was discontinued after 10 days. Thirty days after admission to the hospital a transmetatarsal amputation of the right foot was done with the patient under thiopental (pentothal®) sodium anesthesia. At operation very little bleeding was encountered, but two ligatures being required to insure hemostasis. Old blood clots were seen in the digital arteries. In the ensuing few days a

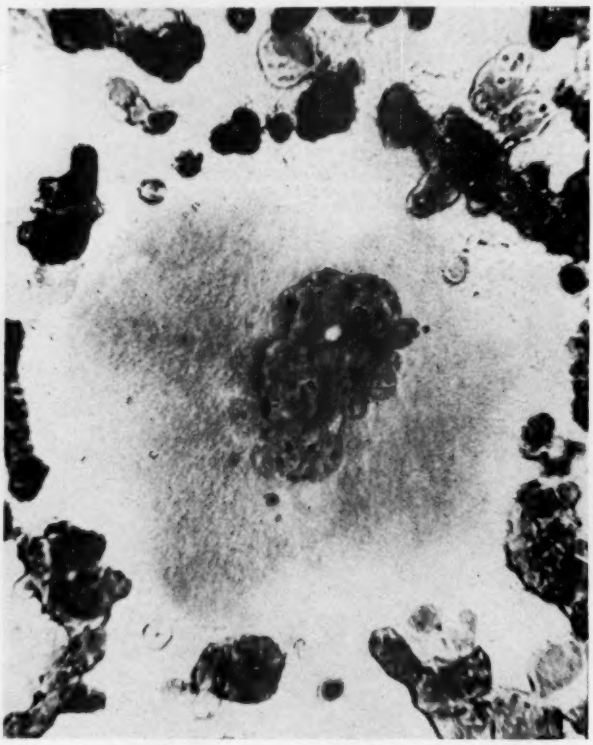

Fig. 5.—Hyperlobulation of a megakaryocyte, as seen in smear of bone marrow aspiration in a patient with essential thrombophilia; × 1,200.

gangrenous process was noted to be developing in the left foot. On the 33d hospital day the patient had an episode of sudden severe crushing substernal pain. He became acutely dyspneic; no heart sounds were audible, and the blood pressure was unobtainable. The patient suddenly died on this day.

Surgical Specimen.—Examination of the surgical specimen (H. F. H. Pathology No. 110403) showed that all the toes and portions of the foot anterior to the first metatarsal were blackened and gangrenous. On microscopic examination, widespread cellular degeneration was evident. In one section there was a large artery, the lumen of which was completely occluded by a thrombus; the wall of this artery was normal in appearance. The thrombus itself showed in its

peripheral portions active invasion by fibroblasts, mononuclear phagocytes, and a few lymphocytes. The central portion contained fibrin, thrombocytes, and a few white blood cells. In the adjacent tissue a second smaller artery showed an old organized thrombus partly occluding the lumen (Fig. 6).

Gross Autopsy Examination.—The body (H. F. H. Autopsy No. 5369) was that of a 65-year-old white man with a broad area of ecchymosis of the left axilla and a midtarsal amputation of the right foot. Dry gangrene of the toes of the left foot was noted. The thighs were of equal circumference.

The heart weighed 480 gm. The coronary vessels showed patchy areas of atherosclerosis, and at one point 7 cm. from the origin of the right coronary artery the lumen of the vessel was

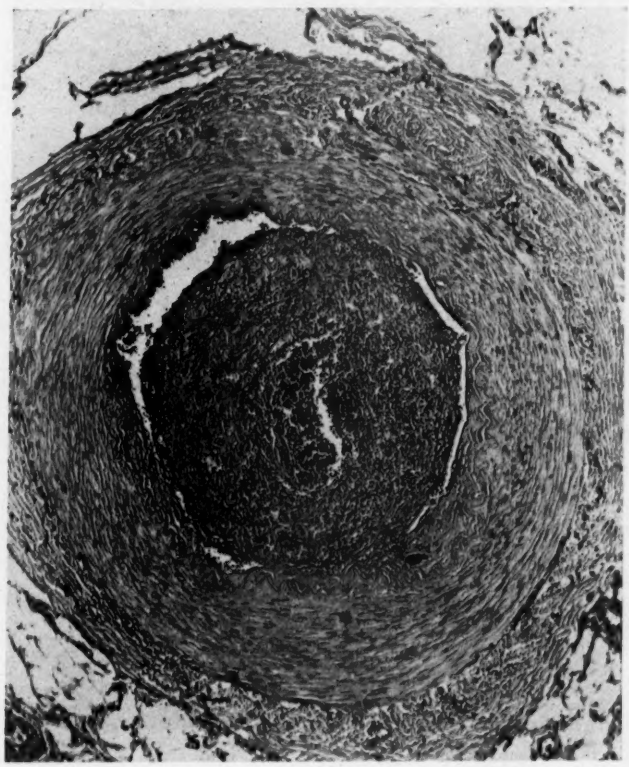

Fig. 6.—Microscopic section of thrombosed artery of foot as seen in essential thrombophilia. Hematoxylin and eosin stain; × 75.

reduced to one-sixth the normal caliber, but there was no evidence of thrombus formation in the coronary system. The myocardium contained a few areas of fibrosis.

A friable red-gray antemortem embolus resembling a cast of a large vein was present in the major pulmonary vessels. Study of the pelvic vessels failed to reveal a source for the embolus. Permission for examination of the leg veins was not obtained.

The right lung weighed 600 gm. The pleural surface of the right lower lobe was thickened, and beneath this area was a triangular firm brownish area typical of an old infarct. The major pulmonary arteries supplying the right upper lobe and the right lower lobe were occluded by a yellow-gray friable thrombus which was attached to the vessel wall.

The left lung weighed 400 gm. In the dependent part of the left lower lobe there was a triangular firm area representing an old infarct. An occasional smaller pulmonary artery contained a granular friable thrombus.

The spleen weighed 440 gm., and the external surface was gray-blue. The organ was firm in consistency, and the cut surface was glistening and reddish-purple. The liver weighed 2,600 gm., and there were a few slightly depressed scars over the capsule. Cross section showed only increased vascular markings. On the anterior surface of the left lobe there was a small triangular area which was deeply hemorrhagic. The left kidney weighed 120 gm. and the right kidney 130 gm. The surface of the kidney was markedly granular when the capsule was stripped

Fig. 7.—Microscopic section of pulmonary artery, illustrating advanced organization of thrombus. Hematoxylin and eosin stain; × 100.

away. There was good demarcation between the cortex and pyramids, the cortex measuring 3 mm. in thickness and the pyramids averaging 1.5 mm. in height. Numerous diverticula were present in the large bowel, and one of these, in the region of the hepatic flexure, was surrounded by an area of inflammation 4 mm. in thickness. The adrenal glands, pelvic organs, and thyroid were not remarkable. The aorta was involved in a mild amount of atherosclerosis, but none of the medium-sized arteries showed abnormal change.

Microscopic Autopsy Examination.—Atherosclerosis of a mild degree was present in the coronary system. The walls of the coronary vessels were in areas lightly infiltrated by a few lymphocytes and plasma cells, and a very few similar cells were present in the fat of the

epicardium and in small areas of the myocardium adjacent to the coronary vessels. A few foci of replacement fibrosis were present in the right ventricular myocardium.

Section of the embolus from the pulmonary artery showed it to be made up of a large number of thrombocytes and fibrin arranged in a laminated fashion, and superimposed on this structure were moderate numbers of white blood cells and red blood cell masses. Examination of the pulmonary thrombus from the right lung showed a well-organized thrombus resting upon a vessel which showed no abnormalities except for a very light infiltrate by lymphocytes and plasma cells in the adventitial region. The thrombus showed far-advanced organization in its peripheral portion with active invasion by fibroblasts and thin-walled capillaries (Fig. 7). Other

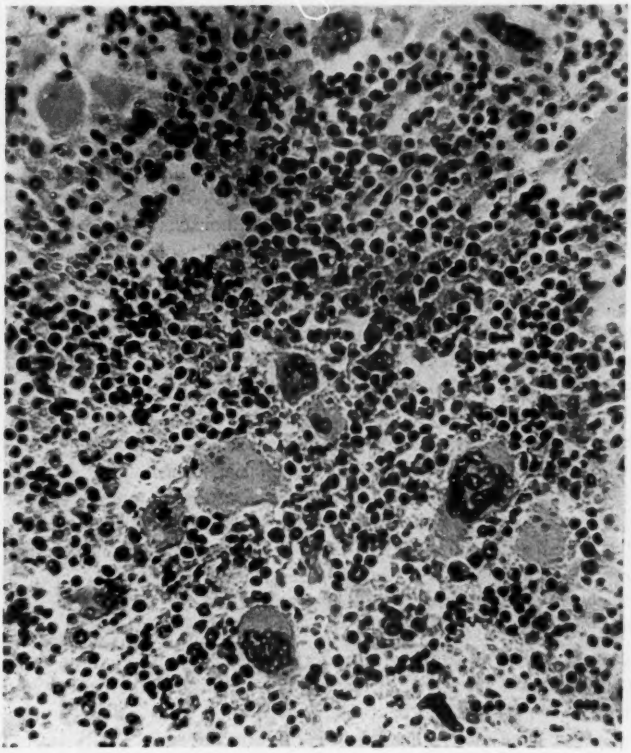

Fig. 8.—Microscopic section of bone marrow, demonstrating marked megakaryocytic hyperplasia in a patient with essential thrombophilia. Hematoxylin and eosin stain; × 320.

thrombosed pulmonary vessels showed a similar picture. The medium-sized arteries of the lungs contained thrombi in varying stages of organization, without change in the vessel walls. There was an increase in thickness of the smaller pulmonary arteries. In the areas of infarct there were active fibroblastic proliferation and blood vessel invasion of the lung parenchyma, with collapse and squamous metaplasia of the bronchi and bronchioles.

The spleen showed congestion of the red pulp. There was an increase in the amount of fibrous tissue, and an occasional siderotic nodule was present. Sclerosis of the vessels which pass through the Malpighian bodies was moderate in amount. In the portal triad areas of the liver there was a slight increase in the number of lymphocytes present, together with a few polymorphonuclear leucocytes. There was vascular congestion. The dark area described in the

gross proved to be a cavernous hemangioma. Except for scattered hyalinized glomeruli and a slight degree of vascular sclerosis, the kidneys presented no lesions. The inflammation about the diverticulum in the hepatic flexure consisted of a heavy infiltration by polymorphonuclear leucocytes, lymphocytes, and plasma cells into the various coats of the bowel wall.

The bone marrow was diffusely hyperplastic. There was, however, a normal differential spread; the most interesting observation was a marked increase in megakaryocytes (Fig. 8). Increased numbers of these cells were present both focally and diffusely.

Anatomic Diagnoses.—The final anatomic diagnoses were (1) arterial thromboses, dry gangrene, right and left foot; (2) multiple pulmonary thromboses, with old infarcts, right and left lungs; (3) massive pulmonary embolism, site of origin undetermined, and (4) bone marrow hyperplasia, with focal and diffuse megakaryocytic hyperplasia.

COMMENT

We believe the case here presented fulfills the criteria set forth by Nygaard and Brown for the diagnosis of essential thrombophilia. Clinically, the patient exhibited an atypical gangrenous process of the feet and signs of pulmonary infarction. There was laboratory evidence of thrombocytosis, increased blood coagulability in vitro, and increase in the globulin and fibrinogen fractions of the plasma proteins. In the microscopic sections thrombus formation was demonstrated in the arteries of the right foot and lungs in the presence of normal vessel walls. There was megakaryocytic hyperplasia of the bone marrow.

The pathological findings obviated the diagnosis of thromboangiitis obliterans. There was no evidence of thrombophlebitis to suggest the syndrome of venous gangrene described by Haimovici.[4] Thrombocytosis excluded the diagnosis of thrombotic thrombocytopenic purpura.

The thrombocytosis was an outstanding feature in this case. Increased numbers of thrombocytes are most frequently encountered secondary to such diseases as acute infections, Boeck's sarcoidosis, myeloid metaplasia, bronchogenic carcinoma, polycythemia vera, severe trauma with hemorrhage, asphyxia, and often splenectomy. There is thrombocytosis in the rare cases of megakaryocytic leukemia. Leitner[5] stated that primary thrombocythemia is a relatively rare condition and can be diagnosed only when in the absence of diseases leading to secondary increase in the thrombocytes there are a threefold increase in the thrombocyte count and megakaryocytic hyperplasia of the bone marrow.

Of unusual interest was the refractoriness to heparin therapy as determined by coagulation times, suggesting a marked abnormality of the patient's coagulation mechanism. The patient's blood tended to gel soon after collection from a vein, making clotting-time determinations difficult to interpret. This phenomenon is better termed pseudocoagulation rather than "hypercoagulation." It is noted, however, that thromboses did not occur while the patient was receiving heparin anticoagulant therapy. DeTakats[6] has reported observations on patients with Buerger's disease (thromboangiitis obliterans), thromboembolism, and thrombophlebitis who did not respond in a normal manner when given test doses of heparin. He designated these persons "hyporeactors" in response to the heparin-tolerance test. Ele-

4. Haimovici, H.: Gangrene of the Extremities of Venous Origin, Circulation **1**:225-240 (Feb.) 1950.

5. Leitner, S. I., and Britton, C. J. C.: Bone Marrow Biopsy, London, J. & A. Churchill, 1949.

6. deTakats, G.: Sensitized Clotting Time, J. A. M. A. **146**:1370-1372 (Aug. 11) 1951.

vation of the plasma globulin and fibrinogen fractions and an increased thrombocyte count have been proposed as the basis for this mechanism and are demonstrated in this case.

Moolten, Vroman, and Vroman [7] have reported briefly on three patients classified as having essential thrombophilia. They believed that these persons demonstrated thrombocyte hyperadhesiveness, indicating intrinsic thrombocyte disease. The intravenous injection of 100 mg. of heparin caused prompt lowering of thrombocyte adhesiveness. Similar reduction in thrombocyte adhesiveness occurred in two patients with thrombocytopenia so treated.

Since cryoglobulinemia has been shown to cause intravascular clotting,[8] resulting in gangrene of extremities when exposed to cold, it is important to note that cryoglobulins were not found in this patient.

SUMMARY

A case of essential thrombophilia studied ante mortem is reported. While heparin therapy did not prolong the coagulation time, thromboses did not occur while the patient was receiving the anticoagulant. Observations on the coagulation mechanisms in this disease are presented.

The bone marrow manifestations of the disease are reported.

Necropsy verification of this disease process is presented.

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7. Moolten, S. E.; Vroman, L., and Vroman, G. M. S.: Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders: Diagnostic and Prognostic Significance of Platelet Adhesiveness, Am. J. Clin. Path. **19**:814-826 (Sept.) 1949.

8. Barr, D. P.; Reader, G. G., and Wheeler, C. H.: Cryoglobulinemia: Report of 2 Cases with Discussion of Clinical Manifestations, Incidence and Significance, Ann. Int. Med. **32**:6-29 (Jan.) 1950.

RESULTS OF CORTISONE-CORTICOTROPIN THERAPY IN CHRONIC ACTIVE RHEUMATIC FEVER

DENNISON YOUNG, M.D.
AND
MANUEL RODSTEIN, M.D.
NEW YORK

STUDIES on cortisone and corticotropin (ACTH) treatment of rheumatic fever have been primarily limited to acute cases of relatively short duration. The beneficial effects first reported by Hench and his associates [1] have been confirmed by subsequent investigators,[2] although more recent reports [3] have served to temper some of the previous enthusiasm. The number of patients with chronic active rheumatic fever so treated is relatively few, and, because of this, observations on, and end-results obtained in, a group of patients of this type treated with large and prolonged dosages of cortisone or corticotropin should be of interest.

MATERIAL

Between June, 1950, and August, 1951, eight children, ranging from 8 to 16 years of age, and suffering from prolonged chronic active rheumatic fever, were treated with cortisone or corticotropin and subsequently followed for 2 to 13 months after cessation of therapy. Six

From the Medical Division (Dr. Louis Leiter, Chief), Montefiore Hospital.

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1. Hench, P. S.; Slocum, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: Effects of Adrenal Cortical Hormone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:227, 1949.

2. (*a*) Massel, B. F.; Warren, J. E., and Sturgis, G. P.: Observations on Effects of ACTH in Patients with Rheumatic Fever and Rheumatic Carditis, Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 405. (*b*) Massell, B. F.; Warren, J. E.; Sturgis, G. P.; Hall, B., and Craige, E.: The Clinical Response of Rheumatic Fever and Acute Carditis to ACTH, New England J. Med. **242**:641 and 692, 1950. (*c*) Massell, B. F., and Warren, J. E.: Effect of Pituitary ACTH on Rheumatic Fever and Rheumatic Carditis, J. A. M. A. **144**:1335, 1950. (*d*) Barnes, A. R., and Smith, H. L.: The Effects of the Administration of Cortisone and ACTH on Patients with Acute Rheumatic Fever, Mod. Concepts Cardiovas. Dis. **19**:59, 1950. (*e*) Barnes, A. R.: Effects of Cortisone and ACTH on the Acute Phase of Rheumatic Fever, Circulation **3**:770, 1951. (*f*) Wilson, M. G., and Helper, H. N.: Effect of Pituitary ACTH on Acute Rheumatic Carditis, J. A. M. A. **145**:133, 1951.

3. (*a*) Harris, T. N.; Abrams, W. B.; Leo, T. F. P., and Hubbard, J. P.: Cortisone Therapy in Acute Rheumatic Carditis: Preliminary Observations, Circulation **3**:215, 1951. (*b*) Kuttner, A. G.; Baldwin, J. S.; McEwen, C.; Bunim, J. J.; Ziff, M., and Ford, D. K.: The Effects of ACTH and Cortisone on Rheumatic Carditis: Observations on 18 Cases, read before the Twenty-Fourth Scientific Sessions of the American Heart Association, Atlantic City, June 8, 1951.

children had been observed by us on a Home Care Rheumatic Fever Program [4] for 8 to 26 months before initiation of therapy and one (Case 3) for a year in the hospital prior to therapy, so that evaluation of a change in the clinical status in relation to treatment was not difficult.

The duration of continued illness in seven patients ranged from 10½ months to five years. In Patient 7 rheumatic fever had been present for at least six weeks, and there was suggestive evidence that the rheumatic process had not been totally quiescent over the preceding 16 months. Some of the patients at the time of admission to the hospital were in a phase of an acute exacerbation superimposed on the prolonged rheumatic activity. All were considered to have chronic active rheumatic fever on the basis of some or all of the following criteria:

1. Clinical Signs

   Malnutrition or failure to gain weight
   Persistent tachycardia
   "General toxicity" manifested by pallor, apathy, lethargy, malaise
   Recurrent paroxysmal arrhythmias
   Congestive heart failure in the presence of rheumatic heart disease
   Recurrent or persistent low-grade fever

2. Laboratory Data

   Persistent anemia
   Persistent elevation of the erythrocyte sedimentation rate in the absence of congestive heart failure
   Electrocardiographic changes, such as P-R interval prolongation or T wave changes

REPORT OF CASES

Case 1.—F. C., an 11-year-old boy, was hospitalized for five months because of severe congestive heart failure in his first attack of rheumatic fever in August, 1949. Over the subsequent eight months at home on a regimen of bed rest, sodium restriction, and frequent administration of mercurials, further deterioration in his condition occurred. When readmitted to the hospital in June, 1950, he was apparently in a terminal phase of his illness. Clinical and laboratory data are shown in Tables 1, 2, and 3.

After a preliminary observation period, treatment was started with cortisone given intramuscularly. The temperature returned to normal in six days; the appetite improved remarkably. A distinct personality change occurred, in that the boy displayed a renewed interest in his medical care and in his future. For the first three weeks of therapy there was no immediate change in the degree of congestive failure, so that frequent treatment with mercurials was still necessary. After this, a progressive decrease in the congestive failure continued without further use of diuretics. The extreme sensitivity to digitalis disappeared. The tachycardia showed a much less dramatic response, and it was not until two weeks after discontinuance of therapy that a distinct and permanent lowering of the heart rate was noted. The heart sounds improved in quality; the murmurs remained unchanged. The anemia gradually disappeared. By the end of therapy a mild polycythemia was present, with the hematocrit reading of 51%. Two weeks after cessation of therapy all evidence of rheumatic fever was gone.

In addition to the common side-effects of prolonged adrenocortical therapy, he had a large furuncle above the right eye requiring incision, drainage, and intensive penicillin administration for two weeks. Healing was very slow. The serum potassium dropped from 4.7 to 3 mEq.; the level was readily restored to normal by the administration of fruit juice and potassium chloride by mouth.

With progressive ambulation there was neither clinical nor laboratory evidence of reactivation of the rheumatic process. A new aortic systolic murmur was heard four months after

4. The Home Care Rheumatic Fever Program was initiated as a pilot project in October, 1948, under a grant from the New York Heart Association.

TABLE 1.—*End-Result of Cortisone-Corticotropin Therapy in Chronic Active Rheumatic Fever*

Patient	1	2	3	4	5	6	7	8
Status before therapy								
Duration of activity	10½ mo.	22 mo.	5 yr.	4 yr.	4 yr.	3 yr.	6 wk.	32 mo.
Cardiac diagnosis*	EH, MI, MS	EH, MI, MS	EH, MI, MS	EH, MI, MS	EH, MI, MS, AI, AS	EH, MI, MS, AI	No heart disease	EH, MI, MS
Therapy								
Drug	Cortisone	Cortisone	Cortisone	Cortico-tropin	Cortisone	Cortisone	Cortisone	Cortisone
No. of days	62	65	85	58	25	21	60	48 54 (102)
Total (mg. IM)	5,200	5,710	5,920	4,770	2,100	2,100	2,950 (IM) 3,250 (oral)	3,440 6,080
Average daily dose	84	88	112	82	84	100	103	77 103
Status immediately after therapy								
Rheumatic activity	Inactive 2 wk. after drug stopped	Inactive 1 mo. after drug stopped	Died	Inactive 2 wk., then active	Active	Active	Active	Active
Cardiac diagnosis*	EH, MI, MS	EH, MI, MS	EH, MI, MS	EH, MI, MS, AI	EH, MI, MS, AI,	EH, MI, MS, AI	EH, MI	EH, MI, MS
Status at maximum follow-up								
Time	13 mo.	12 mo.	..	2 mo.	6 mo.	8 mo.	9 mo.	9 mo.
Rheumatic activity	Inactive	Inactive	..	Active	Active	Inactive	Inactive	Inactive
Cardiac diagnosis*	EH, MI, MS, ?AS	EH, MI, MS, ?AS	..	EH, MI, MS, AI	EH, MI, MS, AI, AS, TI?	EH, MI, MS, AI	No heart disease	EH, MI, MS

* EH means enlarged heart; MI, mitral insufficiency; MS, mitral stenosis; AS, aortic stenosis; AI, aortic insufficiency, and TI, tricuspid insufficiency.

TABLE 2.—*Effect of Cortisone-Corticotropin Therapy on Clinical Manifestations of Rheumatic Activity*

Patient No.; Age, Yr.	Temperature, F.	General Toxicity	Congestive Failure	Heart Sounds	Heart Rate	Gallop Rhythm	Heart Murmurs	Pericarditis	Comment
1 11	101.4 to normal, 6 days	4+ to 0	4+ to 0	Improved	128 to 88	None	No change	None	Marked digitalis toxicity disappeared
2 10	101 to normal, 2 days	4+ to 0	1+ to 3+ to 0	Improved	120 to 80	None	New aortic systolic murmur	Disappeared in 7 days	.....
3 13	Afebrile	4+ to 4+	4+ to 4+	Poor, unchanged	Auricular fibrillation, 112	None	No change	None	Increasing failure to death; digitalis toxicity unchanged
4 12	103 to normal, 11 days	4+ to 0	None	Improved	100 to 90	Disappeared	New aortic diastolic murmur	None	Recurrent supraventricular tachycardia
5 16	103 to normal, 7 days	4+ to 0	4+ to 0	Improved	100 to 60	None	Murmur of tricuspid insufficiency (?) 7 wk. later	None	.....
6 12	103 to normal, 2 days	4+ to 0	None	Poor, unchanged	130 to 80 (2 days)	None	No change	None	Heart rate change along with fever
7 8	No consistent effect	2+ to 2+	None	Fair, unchanged	No consistent effect (88-110)	None	New apical systolic and cardiac enlargement	None	Cyclic temperature elevations to 100.6 F.; digitalis toxicity on therapy
8 12	No consistent effect	4+ to 1+	3+ to 4+ to 0	Poor; moderate improvement	Persistent tachycardia (100-120)	Intermittent	No change	Disappeared in 14 days	Cyclic temperature elevations to 100.6 F.

termination of therapy. Thirteen months after cessation of cortisone administration he was perfectly well. The new aortic systolic murmur was still present. The previously noted marked cardiac enlargement and mitral murmurs were unchanged.

Comment.—This was a patient with severe progressive chronic active rheumatic fever who had entered a terminal phase of his illness with totally refractory congestive heart failure. The dramatic result achieved must be attributed to the cortisone therapy. Despite the disappearance of all signs of rheumatic fever, a new heart murmur developed during the course of therapy.

CASE 2.—K. A., a 10-year-old girl, had her initial attack of rheumatic fever in January, 1949. When first seen in March, 1949, she showed active rheumatic fever with mild chorea and an enlarged heart with mitral stenosis and insufficiency. The chorea slowly subsided and never recurred, but she continued in a chronic active phase of the disease, with the development of congestive heart failure in January, 1950, and of transient auricular fibrillation later. In September, 1950, she was hospitalized with an acute exacerbation of the chronic process, manifested by pericarditis and fever superimposed on long-standing refractory congestive failure. Clinical and laboratory data are shown in Tables 1, 2, and 3.

TABLE 3.—*Effect of Cortisone-Corticotropin Therapy on Laboratory Data**

Patient No.	ECG Evidence of Carditis	E. S. R. (Cutler), Mm./Hr.	RBC, Millions	Hgb., Gm./100 Cc.	WBC	Eosinophile Count	Anti-streptolysin Titer
1	None	6 to 5	5.5 to 6.5	9.8 to 14.5	6,300 to 21,000 to 9,800	.....	400 to 150
2	None	30 to 16	3.2 to 5.0	10.5 to 13.5	13,000 unchanged	110 to 11	.....
3	None	5 to 3	3.95, unchanged	11.5 to 12.5	10,000 unchanged	99 to 33	100
4	P-R, 0.21 to 0.12 sec.	30 to 14	3.2 to 4.7	9.8 to 13.5	9,750 to 17,750 to 9,400	66 to 0	150
5	None	32 to 25	3.2 to 4.0	9.8 to 12.4	9,700 to 18,900 to 7,750	88 to 44	1,000 to 250
6	P-R 0.20 sec. unchanged	28 to 22 to 30	3.7	11.5	10,350 to 25,000	143 to 22	.....
				Acute blood loss (ulcer)			
7	P-R 0.18 to 0.14 sec.	29 to 15 to 23	3.3 to 4.6	9.75 to 12.5	3,400 to 14,300 to 6,650	99 to 44	500 to 250
8	T-wave changes, pericarditis (41 days)	36 to 6 to 36	3.3 to 4.0	9.8 to 12.5 to 11.5	8,000 to 13,400	99 to 22	100

* ECG indicates electrocardiagraphic; E. S. R., erythrocyte sedimentation rate; RBC, red blood cells; Hgb., hemoglobin, and WBC, white blood cells.

After six days intramuscular administration of cortisone was started. The temperature returned to normal in two days. She had a definite sense of well-being, with a marked disappearance of her previous apathy. The appetite improved greatly. Initially there was an increase in the degree of fluid retention, with further enlargement of the liver and the development of peripheral edema. With persistence of therapy, the congestive failure slowly disappeared and use of mercurials was no longer necessary. The pericardial rub disappeared in seven days. The tachycardia slowly diminished, but the heart rate did not return to normal until two weeks after cessation of therapy. The quality of the heart sounds gradually improved. Over a two-month period the red blood cell count, the hemoglobin concentration, and the erythrocyte sedimentation rate slowly returned to normal. Rebound phenomena, characterized by mild fever, anorexia, headache, and malaise, occurred for three days after treatment with the drug was discontinued. The only important side-effect was increased fluid retention shortly after institution of therapy.

The rheumatic process was considered completely inactive one month after cessation of therapy. The apical murmurs and the degree of cardiac enlargement had not changed. (There had never been roentgenographic evidence of pericardial effusion.) An aortic systolic murmur

was noted for the first time one month after institution of therapy. No evidence of rheumatic fever occurred over the subsequent 12-month period of observation. The heart remained markedly enlarged with the same apical murmurs, and the newly developed aortic systolic murmur persisted.

Comment.—The rheumatic process seemed interminable and the course progressively downhill in this patient prior to institution of treatment. In view of the rather distinct change in the clinical status following cortisone therapy, it must be concluded that this was probably the responsible factor for the remarkable improvement. Despite this gratifying result, additional evidence of valvular involvement developed during cortisone administration.

Case 3.—A. S., a 13-year-old girl, with a 10-year history of chronic active rheumatic fever and numerous bouts of congestive heart failure, was admitted to the hospital in October, 1949. There had been no remission in her status for at least five years. She remained in chronic congestive failure during the entire one-year period of hospitalization, despite all the usual therapeutic measures. Clinical and laboratory data are shown in Tables 1, 2, and 3. Attempts to slow the ventricular rate were repeatedly unsuccessful because of marked sensitivity to digitalis.

Her course continued progressively downhill, with increasing manifestations of heart failure. Her condition was considered terminal when cortisone treatment was started. During the period of therapy the congestive failure increased, so that repeated abdominal paracenteses and constant administration of oxygen became necessary. The general toxicity, heart sounds, and murmurs remained unchanged. The digitalis sensitivity persisted. The serum potassium dropped from 6.3 to 3.2 mEq. despite oral administration of potassium chloride and fruit juices. No other side-effects of the drug therapy were noted, except perhaps the increased degree of congestive failure, which was more likely due to the progressive course of the disease. She died while still receiving cortisone therapy.

At postmortem examination (performed by Dr. Russel Sherwin) the heart weighed 500 gm. and showed evidence of a healed rheumatic auriculitis, valvulitis, and pericarditis. All lobes of the lung revealed chronic passive congestion with moderate edema and patchy atelectasis. The lower lobes contained discrete and coalescent zones in which the interalveolar septa were densely fibrotic and generally thickened. Many medium-sized and small arteries and arterioles in all lobes showed hyperplastic sclerosis, as reflected by concentric fibrous intimal thickening and medial hypertrophy, resulting in a variable degree of narrowing of their lumens. A more striking change was noted in multiple medium and small arteries; they were severely narrowed to almost completely occluded as a result of extreme circumferential thickening of their walls, especially of the intima. The endothelium was swollen. The lumens of some were surrounded by loose fibrous tissue containing collections of large irregular mononuclear cells and lymphocytes and an occasional thin-walled capillary. In places this alteration extended into the media, replacing muscle. In other vessels a broad subendothelial layer of highly vascular connective tissue, containing numerous dilated thin- and thick-walled vascular channels of capillary caliber, was noted. In some of these a sparse scattering of mononuclear inflammatory cells persisted. The demarcation of intima from media was frequently obliterated. Wide bands of dense collagenous connective tissue resulted in thickening of the adventitia.

The final anatomical diagnoses were healed rheumatic mitral and tricuspid valvulitis, auriculitis, and pericarditis; mitral stenosis and insufficiency; dilatation and hypertrophy of the heart; chronic passive congestion of lungs, liver, and spleen; ascites; edema of lower extremities; pulmonary arteriosclerosis; healed and healing rheumatic pneumonitis and pulmonary arteritis; organizing thrombus in main subdivision of left pulmonary artery.[5]

Comment.—Cortisone therapy was obviously ineffective. It cannot be stated with assurance that the demonstration of healed and healing rheumatic lesions is attributable to the administra-

5. Dr. James Berkman carefully reviewed the pathological material. This was presented by Dr. Berkman and Dr. C. Shim at a meeting of the New York Pathological Society, Nov. 29, 1951, in a paper entitled "Pulmonary Rheumatic Arteritis."

tion of cortisone. The total inefficacy of the drug may perhaps be attributed to inadequate dosage for this patient. It is more likely that the extremely advanced stage of the disease rendered her refractory to any type of therapy.

CASE 4.—A. T., a 12-year-old boy, had been repeatedly hospitalized because of chronic active rheumatic fever over a four-year period. When he was first seen in February, 1949, there was clinical and laboratory evidence of chronic rheumatic activity. Between June, 1950, and March, 1951, recurrent episodes of paroxysmal supraventricular tachycardia occurred. In April, 1951, he had an acute exacerbation of the chronic active process, for which he was hospitalized. Clinical and laboratory data are shown in Tables 1, 2, and 3.

After preliminary observation treatment was started with corticotropin. The temperature dropped to normal in 11 days, but during a two-day period of omission of the drug it rose to 102 F., to return to normal two days after resumption of therapy. The general toxicity disappeared, appetite improved, and a sense of well-being developed. The heart rate never changed appreciably, but the gallop rhythm disappeared, and the quality of the heart sounds improved. An aortic diastolic murmur was first heard on the 47th day. The P-R interval, the erythrocyte sedimentation rate, the hemoglobin concentration, and red blood cell count returned to normal.

In addition to the common side-effects of prolonged adrenocortical stimulation, occasional glycosuria with normal blood sugar levels was noted. The serum potassium dropped to 2.2 mEq. but was restored to normal after discontinuance of the corticotropin therapy for two days and the oral administration of potassium chloride and orange juice. Corticotropin was again given daily thereafter, and the large oral doses of potassium salt were continued. The course continued uneventful as the manifestations of rheumatic activity slowly disappeared. On discontinuance of the drug therapy there occurred a three-day period of typical withdrawal manifestations and on the third day a paroxysm of supraventricular tachycardia.

The rheumatic process then became quiescent by clinical and laboratory evaluation for a two-week period, but thereafter the patient showed an intermittent rise in temperature, an increase in the erythrocyte sedimentation rate, and persistence of sinus tachycardia. Two months after use of the drug had been discontinued, he still showed low-grade rheumatic activity. The cardiac findings were unchanged, with the newly developed aortic diastolic murmur still present.

Comment.—This patient had long-standing chronic active rheumatic fever. Prolonged corticotropin therapy seemed to suppress many but not all of the manifestations of activity. Specifically the carditis was not suppressed, for, despite a return of the P-R interval to normal, aortic insufficiency developed while he was receiving treatment. Shortly after the corticotropin therapy was discontinued, his status was no different from what it had been during most of the previous two years.

CASE 5.[6]—M. R., a 16-year-old boy, had had chronic active rheumatic fever with constant mild congestive heart failure over at least a four-year period prior to admission. He was hospitalized because of an acute exacerbation with increased congestive failure over the previous three weeks. Administration of digitalis and mercurials had not improved the clinical status. Clinical and laboratory data are shown in Tables 1, 2, and 3.

During the first two weeks in the hospital he required frequent use of mercurials and bilateral thoracenteses, after which cortisone therapy was started. A distinct sense of well-being and improvement in appetite quickly occurred. The temperature returned to normal in seven days. Over the same period the heart rate dropped to 88 beats per minute and then slowly decreased further to a rate of 60, a level which persisted for only two weeks after therapy was stopped. Marked improvement in the congestive failure rapidly occurred, and all signs were gone by the time therapy was concluded. The heart size and murmurs did not change. The erythrocyte sedimentation rate dropped slightly and remained at this level. Moderate improvement in the anemia occurred. The leucocytosis which developed with the therapy receded when use of the drug was discontinued. Adiposity and the typical moon facies were the only side-effects noted.

6. M. R. was a private patient of Dr. John B. Schwedel.

Despite remarkable improvement with a relatively short course of cortisone therapy, active rheumatic fever was still present at time of discharge and for the subsequent six months that the patient was followed. One month later, the liver was again enlarged and the erythrocyte sedimentation rate was further elevated. Thereafter the liver became progressively larger despite treatment with mercurials and sodium restriction. Seven weeks after cessation of therapy a new systolic murmur to the right of the lower sternum was heard; this was interpreted as probably representing tricuspid insufficiency. The other cardiac findings remained unchanged; the newly developed murmur persisted.

Comment.—The effect on the congestive heart failure in this patient was striking. Despite the apparent improvement in myocardial function, in all probability attributable to the cortisone therapy, the rheumatic process remained active. Perhaps this could have been rendered inactive had therapy been more prolonged. The new murmur, which was assumed to suggest the presence of tricuspid insufficiency, does not necessarily indicate the additional development of organic disease of the tricuspid valve. The cortisone treatment apparently tided him over a critical period of severe congestive heart failure.

CASE 6.—G. S., a 12-year-old boy, had had evidence of chronic active rheumatic fever with recurrent congestive heart failure for at least three years. He then had a superimposed acute exacerbation, for which he was hospitalized. Clinical and laboratory data are shown in Tables 1, 2, and 3.

Cortisone was administered for 21 days, and then therapy was stopped because of massive gastrointestinal hemorrhage, roentgenographically shown to be due to an active duodenal ulcer. The temperature dropped to normal in 48 hours, and along with this decrease the heart rate was reduced from 130 to 80 beats per minute. The general toxicity improved fairly rapidly, and a sense of well-being with increased appetite ensued. The poor quality of the heart sounds, the murmurs, and the heart size remained unchanged. The prolonged P-R interval was not affected. The erythrocyte sedimentation rate fell slightly but shortly thereafter rose again and remained at the elevated level. The actual effect on the red blood cell count and hemoglobin concentration could not be determined because of melena. The leucocytosis may have been secondary to the bleeding rather than to the cortisone therapy. In addition to the probable activation of a duodenal ulcer, the common side-effects of cortisone therapy also occurred.

During two months of observation in the hospital following discontinuance of the drug administration, the rheumatic process continued with the same degree of chronic activity manifested prior to the acute flare-up. On follow-up observation a gradual regression of the clinical and laboratory manifestations of rheumatic activity occurred. Roentgenographic evidence of the duodenal ulcer persisted for five months. Eight months after conclusion of therapy, there was no evidence of active rheumatic fever. The cardiac findings were unchanged.

Comment.—Benefit was obtained in this patient by virtue of the nonspecific effect of cortisone on the general toxicity accompanying his illness. No effect on the basic illness, specifically on the degree of carditis, was obtained. In addition, a severe side-effect with potentially serious outcome occurred. The eventual termination of rheumatic activity seemed to be a function of time rather than of therapy, although it may be argued that had it not been necessary to terminate cortisone treatment because of the duodenal hemorrhage, more rapid quiescence might have been achieved.

CASE 7.—P. T., an 8-year-old boy whose initial attack of rheumatic fever lasted one year, was hospitalized in November, 1950, because of a six-week exacerbation of rheumatic activity. Clinical and laboratory data are shown in Tables 1, 2, and 3.

After a preliminary observation period cortisone therapy was started. The moderate degree of general toxicity remained unchanged; the marked appetite also remained unchanged. There was no consistent effect on the fever, there being frequent slight temperature rises to 100.4 or 100.6 F. Two days after treatment with the drug was discontinued, however, the temperature rose to 101.5 F., and thereafter daily for a week to 101 F. It then again dropped to nearer normal with intermittent rises to 100.4 or 100.6 F. The heart rate never showed a distinct lowering; the quality of the heart sounds did not change. An apical systolic murmur became more intense, and with it roentgenographic evidence of enlargement of the left ventricle and

left auricle developed. The P-R interval decreased. The erythrocyte sedimentation rate dropped to normal in a month and then, while he was still receiving cortisone, rose to a mildly elevated level of 18 mm.; immediately after cessation of therapy it rose further to 23 mm., at which level it persisted. The hemoglobin concentration and the red blood cell count slowly increased to normal. At the cessation of therapy his clinical status was fundamentally unchanged, and he showed evidence of cardiac involvement that was not present prior to the institution of therapy. During the subsequent one-month period of observation in the hospital, no further change occurred. The common side-effects of prolonged cortisone therapy developed. Definite personality alterations were evidenced by a change from a pleasant docile boy to an aggressive one who fought with his roommate and abused the nurses.

After discharge there were slight daily rises in temperature and persistent clinical and laboratory evidence of rheumatic activity. The apical systolic murmur was unchanged. Two months after cortisone therapy had been discontinued, a new systolic murmur in the aortic area became audible. With a restricted regimen for five months there was no change in status. Shortly after ambulation was started, the fever permanently disappeared, the tachycardia diminished, the sedimentation rate fell to normal, and a feeling of well-being appeared. Nine months after cessation of cortisone therapy, there was no evidence of rheumatic activity. There was only a faint systolic murmur at the apex, and roentgenographically no cardiac chamber enlargement was seen.

Comment.—In this patient with low-grade chronic rheumatic activity cortisone therapy had apparently no significant effect on either clinical or laboratory manifestations. The total course and duration of the disease seemed to be unaffected, and the impression was that the end-point of quiescence was achieved as a natural remission rather than by virtue of the adrenocortical therapy. Evidence of presumable organic cardiac involvement which developed during therapy receded many months after therapy had been discontinued.

Case 8.—A. G., a 12-year-old boy, showed rapid development of severe congestive heart failure in his first known attack of rheumatic fever in March, 1949. Rheumatic fever with congestive failure persisted during a 26-month period of observation. There were short intervals of moderate remission when rigid sodium restriction and administration of mercurials were not necessary. A superimposed acute flare-up started three weeks prior to admission. Clinical and laboratory data are shown in Tables 1, 2, and 3.

After cortisone therapy was started, there was no consistent effect on the low-grade fever. An increased sense of well-being and increased appetite occurred, but, in general, diminution in the degree of toxicity was only moderate. The tachycardia was never fully abated. Although the pericardial friction rub disappeared in 14 days, the T wave inversions on the electrocardiogram persisted for 41 days. The heart sounds showed moderate improvement; the gallop rhythm recurred intermittently. There was no change in the murmurs or in the size of the heart. The degree of congestive failure initially increased during treatment, but then slowly the signs of failure disappeared. When digitalis was given during this period of increased failure, toxicity developed. The erythrocyte sedimentation rate slowly diminished, but toward the end of the first course of therapy, when smaller doses were given (10 mg. per day), it again started to rise.

During a 10-day period that cortisone administration was discontinued, his general condition remained the same, although the degree of fever was slightly more marked and the sedimentation rate was increased. A second course was instituted, during which there was no striking change in the clinical status. Digitalis intoxication again occurred. The sedimentation rate returned to normal. The hemoglobin concentration, which had risen during the first course, dropped slightly, but the red blood cell count remained unchanged.

Shortly after institution of therapy persistent glycosuria developed. Fasting blood sugar levels were always normal. The dextrose-tolerance curve showed an initial blood sugar level of 61 mg. per 100 cc., rising to 93 mg. in one hour and then returning to 63 mg. by the second hour. The other common side-effects of prolonged adrenocortical therapy also developed.

For the subsequent two months after cessation of treatment there was no further change in his status. The general condition and laboratory data remained about the same, although con-

gestive failure did not recur. He was still considered to have chronic active rheumatic fever when he was transferred to Irvington House, Irvington, N. Y. There [7] he continued to manifest persistent tachycardia and elevation of the erythrocyte sedimentation rate for another four months. At this time these manifestations of activity returned to normal, but the electrocardiogram showed a P-R interval of 0.20 second compared with a previous P-R interval of 0.18 second. Nine months after cortisone treatment had been stopped, he appeared clinically well. The cardiac findings were unchanged. The hematological data were normal. The P-R interval was still 0.20 second. In the absence of other clinical or laboratory abnormalities this is assumed to represent a fixed change due to previous cardiac damage rather than an indication of existent rheumatic activity.

Comment.—An excellent result was achieved in this patient in regard to permanent disappearance of the congestive failure despite the persistence of rheumatic activity. The total duration of active rheumatic fever seemed to have been unaffected, however, and the termination of activity appeared to have been a function of time rather than a result of the prolonged adrenocortical therapy.

RESULTS

In evaluating the effect of therapeutic agents on a disease process, there is a tendency to forget the natural course of the disease in the initial enthusiasm of apparent accomplishment. This may be true particularly of an illness such as rheumatic fever which may pursue a short benign or fulminating course or a long progressive course with an eventual natural spontaneous remission. Unfortunately, the end-point of any type of rheumatic cycle is unpredictable, so that if a new drug is administered near this end-point in the natural course of the disease a miraculous "cure" may result.

An attempt to arrive at a conclusion on the effectiveness of adrenocortical therapy in chronic active rheumatic fever requires consideration of two possibilities: (1) that treatment actually results in a disappearance of the rheumatic process and all evidence of carditis, and (2) that the subsidence of evidence of rheumatic activity is a function of time rather than of any changes wrought by the hormone therapy, even though the level of intensity of symptoms may be lowered.

General Evaluation of Therapeutic Effect (Table 1).—Of the eight patients treated with adequate daily doses of the drug as evaluated by the eosinophile response,[8] in only two (Cases 1 and 2) was all evidence of rheumatic activity gone shortly after termination of therapy and for a prolonged period thereafter. In four patients (Cases 5, 6, 7, and 8) the active rheumatic process continued throughout the period of hormone administration and for many months thereafter, and in one patient the process reactivated after two weeks of apparent quiescence. One patient (Case 3) died while receiving treatment. Postmortem examination showed a healed and healing rheumatic pneumonitis and arteritis.

In Case 1, admitting the variability of even severe rheumatic fever with marked congestive heart failure and not infrequently spontaneous remission, administration of the drug seemed to have been lifesaving. When use of the drug was started, the child's status was progressively deteriorating and he was refractory to all usual

7. Observations at Irvington House were supplied by Dr. Gene Stollerman.

8. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005, 1948.

therapeutic measures. Death seemed to be but a matter of a short time prior to institution of cortisone therapy. The response was dramatic and has apparently been sustained.

An excellent result was also achieved in Case 2, although mild doubt may exist concerning the factors responsible for the remission. That this could be spontaneous concomitant with cortisone therapy is not deniable, but on comparing her present state of well-being with her status during the 22 months of chronic active rheumatic fever prior to therapy, it would not be self-deceptive to attribute the result to cortisone treatment. This patient, too, has continued well over a 12-month follow-up period.

Effect on Individual Symptoms and Signs (Table 2).—In general, the nonspecific effects of adrenocortical hormone therapy observed in these patients were similar to those that have been noted previously in rheumatic fever and many other diseases. Marked diminution in the degree of "general toxicity," a greater sense of well-being apart from concomitant additional clinical improvement, and the common antipyretic effect occurred as a rule but not consistently in all patients. The degree of improvement in these manifestations did not necessarily correlate with the severity of the disease process, the degree of toxicity, or the height of the fever.

The effects on the various manifestations of carditis were not striking. The pericarditis in two patients seemed to disappear no more rapidly than has been frequently noted in this disease with salicylate therapy or without therapy. The quality of the heart sounds improved in five patients, but in three there was no significant change. Of two patients with gallop rhythm, in only one did this manifestation disappear. The tachycardia returned to a normal rate in only half the patients, and in only one did a mild degree of bradycardia occur. Digitalis sensitivity was unchanged in one patient, disappeared in one, and appeared in one patient during therapy.

In seven of the eight patients the murmurs present prior to therapy remained unchanged. In two (Cases 2 and 4) additional persistent aortic murmurs developed during the period of treatment, and in one (Case 1) four months later. One patient (Case 7), who had no clinical evidence of organic heart disease at initiation of therapy, exhibited a moderately loud apical systolic murmur and roentgenographic evidence of enlargement of the left ventricle and left auricle while receiving cortisone. Seven months after therapy had been discontinued, however, there was again no evidence of presumptive organic heart disease.

Most striking was the effect on congestive heart failure. Cortisone was the drug of choice in such patients because it has less tendency to promote salt and water retention than corticotropin has. Five patients were in congestive failure at the time the drug was first given. In two the degree of failure increased initially, and in two there was a fairly long latent period before a diminution in the degree of failure was apparent. During the early phase, therefore, the maintenance of a low-sodium diet and the frequent use of mercurial diuretics were necessary. Once regression of the failure became definitely established, the administration of mercurials was no longer required, and after all evidence of failure had disappeared the restricted diet was also no longer necessary. In the patient who died, the congestive failure increased during the 35 days of cortisone therapy. Both clinically and pathologically rheumatic fever persisted.

Effect on Laboratory Manifestations of Rheumatic Activity (Table 3).—Once again, in contrast to the strikingly rapid changes in results of laboratory studies that have been noted in the more acute phases of rheumatic fever, the changes were not striking in a number of our patients and were never rapid in those that did show a return to normal. The T wave inversions due to pericarditis in one patient persisted for 41 days of therapy. In two patients the P-R interval slowly returned to normal, while in one it remained prolonged throughout. Two patients in congestive failure had normal erythrocyte sedimentation rates throughout. In two the sedimentation rate very slowly reached normal levels by the time the course of therapy was terminated. The others showed no persistent significant change.

Except for the patient who died and the patient who suffered severe blood loss from the bleeding duodenal ulcer, the anemia was corrected in all. In fact, one patient (Case 1) showed polycythemia at the end of his course of cortisone therapy, with a hematocrit reading of 51%. As a rule leucocytosis developed secondary to

TABLE 4.—*Side-Effects of Prolonged Cortisone-Corticotropin Therapy*

Side-Effect	No. of Cases
Moon facies	7
Adiposity	7
Gynecomastia	6
Hirsutism	5
Striae	3
Hypertension	3
Hypokalemia	3
Glycosuria	2
Increase in failure	2

Peripheral edema, acne, pigmentation, furunculosis, delayed wound healing, duodenal ulcer, mental changes, and polycythemia occurred once each.

the adrenocortical treatment. When adequately followed, a drop in the antistreptolysin titer was found.

Side-Effects of Therapy (Table 4).—The only serious side-effect that occurred was the apparent activation by cortisone of an unsuspected, previously asymptomatic duodenal ulcer resulting in massive gastrointestinal bleeding in a 12-year-old boy (Case 6). Roentgenographic evidence of active duodenal ulceration persisted for the subsequent five months, and even then, although anemia was no longer present, occult blood was still present in the stool.

The other side-effects were of less clinical significance, were relatively transient, and occurred with about the same incidence as that reported by others,[9] with a few exceptions. Only one child showed the development of a very mild facial acne on prolonged drug administration. The incidence of gynecomastia was unusually high, all six boys showing this phenomenon, whereas it occurred in neither of the girls. A nine-month persistence of striae in Patient 8 was also somewhat unusual. At this time all other manifestations of hypercortisonism had disappeared.

9. Rosenberg, I. N.; Cleroux, A. P.; Raben, M. S.; Payne, R. W., and Astwood, E. B.: Clinical Evaluation of Corticotropin Therapy, A. M. A. Arch. Int. Med. **88**:211, 1951.

The glycosuria that occurred in two of the patients was apparently related to a lowering of the renal threshold by hormonal therapy, for in both patients normal blood sugar values were always present. Lowering of the serum potassium due to increased renal potassium excretion occurred in three of the eight patients, despite attempts to prevent this by a large intake of orange juice and potassium salt orally. In none of these patients was the hypokalemia considered of clinical significance.

Rebound phenomena were observed in two children after discontinuance of hormone therapy. In Patient 2, there was a very mild three-day episode characterized by slight fever, malaise, headache, and anorexia. In Patient 4 there was a three-day elevation of the temperature, a marked increase in the erythrocyte sedimentation rate, and on the third day an episode of paroxysmal supraventricular tachycardia. Both these patients had received smaller doses of the drug in the concluding days of therapy in a tapering-off process intended to avoid rebound manifestations.

TABLE 5.—*Collected Results of Adrenocortical Therapy in Chronic Active Rheumatic Fever*

Author	No. of Cases	Immediate Effect			Later Follow-Up
		Rheumatic Activity	Cardiac Murmurs	Congestive Failure	
Massell and others [2b]..	4 (Cases 2, 3, 9, 10)	2 active 1 inactive 1 ? active	Unchanged in all	Present in 4 Cleared in 3	1 active at 4 mo. 1 active at 3½ mo. 2 no data
Kuttner and others [3b]..	6 (Cases 8-12, 18)	6 active	4 unchanged 1 new apical diastolic 1 lost apical diastolic	Present in 2 Cleared in 2	4 inactive 1 active at 3 mo. 1 active at 12 mo.
Spain and Roth [18].....	1	Died; necropsy: active rheumatic pancarditis; congestive heart failure			
Dorfman and others [11]	12 (Cases 1-11, 18)	11 active 1 "probably active"	Unchanged in all 1 new aortic diastolic	Present in 8 Cleared in 7	6 inactive 5 active 1 died (active)
Fischel [12]	8	7 active	Data not given on all		
Young and Rodstein...	8	5 active 2 inactive 1 died (active)	Unchanged in all 4 new murmurs (1 aortic diastolic 2 aortic systolic 1 apical systolic with cardiac enlargement)	Present in 5 Cleared in 4	6 inactive 1 active 1 died (active)

COMMENT

The results in these eight patients are similar to those in the small number of cases of chronic active rheumatic fever recorded in the literature (Table 5). If we arbitrarily choose a six-week period of rheumatic activity as the dividing line between "acute" and "chronic," 4 of the cases of Massell's group,[2b] 6 of Kuttner's group,[3b] 12 of Dorfman's group,[11] 8 described by Fischel,[12] and the autopsied case

10. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relations to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**:651, 1948. Kass, E. H.; Ingbar, S. H., and Finland, M.: Renal Glycosuria Induced by Adrenocorticotrophic Hormone, Proc. Soc. Exper. Biol. & Med. **73**:669, 1950. McEwen, C., in discussion on Stillman, J. S., and Bayles, T. B.: Effect of ACTH on Juvenile Rheumatoid Arthritis or Still's Disease, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 402.

11. Dorfman, A.; Bergenstal, D. M.; Smull, K.; Howard, R.; Senz, E.; Oleson, D., and Muller, R.: The Effect of ACTH on Rheumatic Fever, in Proceedings of the Second Clinical ACTH Conference, Vol. II: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, p. 645.

12. Fischel, E. F., in discussion on Dorfman and others,[11] p. 662.

reported by Spain and Roth [13] are comparable with ours. In almost all these collected cases the rheumatic process had been active much longer than the arbitrarily chosen six weeks.

Of this total of 39 cases, clinical evidence of rheumatic activity definitely persisted after therapy in 32, was questionably still present in 2, was observed at postmortem examination in 2, and had disappeared in only 3. Thus, it would appear that in chronic active rheumatic fever one cannot anticipate a total disappearance of the active process on the use of adrenocortical therapy.

Nevertheless, definite benefit can be achieved in the severely ill rheumatic child, especially in the alleviation of congestive heart failure, which is often so extremely resistant to the usual therapeutic measures and may result in death. Of the 39 patients, 20 were in congestive failure at the time therapy was initiated. Failure cleared in 16 and persisted in the other 4. Intensification of the severity of the failure in the early period of therapy is frequent, but is no contraindication to continuation of treatment with the drug if a sodium-restricted diet is maintained and adequate use is made of the mercurial diuretics. The effectiveness of digitalis in the presence of auricular fibrillation following initiation of adrenocortical therapy was noted by Massell,[2b] but our experience was not similar.

The adrenocortical effect on the myocardium will, as a rule, improve cardiac function even in those cases in which all evidence of an active rheumatic carditis does not disappear, so that the heart will once again be able to maintain the circulatory load. Striking, too, has been the observation that in none of those children who still showed persistent prolonged evidence of active rheumatic fever after the congestive failure was cleared, either in our series or in the collected group, did failure recur. The severity, if not the duration, of the disease is apparently diminished.

It is not surprising to find that in no one's experience with chronic active rheumatic fever has there been regression in heart size and rarely in the cardiac murmurs, for the degree of heart disease was fairly well established at the time therapy was initiated. The appearance of new significant murmurs in a number of treated patients with the chronic active disease, as well as in those [3b] treated at a much earlier phase of the disease process, tends to cast doubt on the optimism voiced particularly by Massell [2b] and by Wilson [2f] concerning the potential value of these drugs in preventing cardiac involvement. The inference cannot be drawn that, because the severity of the disease process is diminished, the degree of ultimate cardiac involvement will be lessened.

The other symptomatic effects of adrenocortical therapy in this group of patients were probably nonspecific but are important in the treatment of chronic illness. Most of the children felt better shortly after initiation of treatment; the appetite improved; apathy diminished. Fever was not consistently affected in all. In general, the sicker the child at the time treatment with the drug was started, the greater and the more rapid was the degree of symptomatic improvement, exclusive of the manifestations of congestive failure.

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13. Spain, D. M., and Roth, D.: Effect of Cortisone and ACTH on the Histopathology of Rheumatic Carditis: Report of a Necropsied Case, Am. J. Med. **11**:128, 1951.

When laboratory findings showed a return to normal in our group of patients, this was always much slower than in the acute type of the disease and even slower than in the patients with the chronic active disease previously described. Most consistent was the slow disappearance of the anemia and the development of a leucocytosis secondary to adrenocortical therapy, thus precluding the use of the white blood cell count as evidence of an active phase of the disease process.[14]

In view of an inability to demonstrate that all patients with chronic active rheumatic fever will necessarily benefit from adrenocortical therapy, greater attention must be paid to the potentially harmful effects of these drugs. In general, the common side-effects have little clinical significance, but some others may. Although no previous reports of duodenal ulceration subsequent to this type of therapy in children have appeared and evidence [15] for a causal relationship is not wholly convincing, massive gastrointestinal bleeding was considered an indication for prompt discontinuance of use of the drug. Hypokalemia, too, is of potential clinical significance and is not always preventable even when adequate additional amounts of potassium and potassium-containing foods are administered.

SUMMARY

Eight children with chronic active rheumatic fever were treated with cortisone or corticotropin (ACTH) for prolonged periods. One patient died while still receiving cortisone and at autopsy showed an active, healing rheumatic process in the lungs. In five patients the process continued to be active after cessation of therapy, and in none of these patients was the total duration of the disease apparently shortened, although the severity of the disease was definitely diminished in four. One patient, desperately ill, was considered to have had his rheumatic process terminated by therapy and has remained in good health for more than a year. In one other patient, in all probability, a severe rheumatic process was also terminated by therapy with no reactivation over a year's time. Congestive heart failure refractory to all other therapeutic attempts was cleared entirely in four of five patients.

In no patient was the degree of cardiac involvement diminished by virtue of therapy. Four patients displayed evidence of additional organic heart disease during or shortly after treatment, although in one, seven months after cessation of therapy, there was again no clinical evidence of cardiac involvement. In the other three the additional murmurs persisted on the follow-up examinations.

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14. Rosenberg and others.[9] Hain, K., and Wilson, M. G.: Immunologic and Biochemical Studies on Infants and Children with Special Reference to Rheumatic Fever: VIII. Response to Pituitary Adrenocorticotropic Hormone (ACTH), Pediatrics **4**:579, 1949.

15. Beck, J. C.; Brown, J. S. L.; Johnson, L. G.; Kennedy, B. J., and MacKenzie, D. W.: Occurrence of Peritonitis During ACTH Administration, Canad. M. A. J. **62**:423, 1950. Habif, D. V.; Hare, C. G., and Glazer, G. H.: Perforated Duodenal Ulcer Associated with Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **144**:996, 1950. Kuzell, W. C., and Schaffarzick, R. W.: Cortisone Acetate in 32 Cases: Preliminary Clinical Observations, Stanford M. Bull. **8**:125, 1950. Sprague, R. G.: Cortisone and ACTH: A Review of Certain Physiologic Effects and Their Clinical Implications, Am. J. Med. **10**:567, 1951. Smyth, G. A.: Activation of Peptic Ulcer During Pituitary Adrenocorticotropic Hormone Therapy, J. A. M. A. **145**:474, 1951.

The usual nonspecific effects of adrenocortical therapy on fever and general well-being were observed in the majority of patients but not in all. All the common side-effects of these drugs were also observed and are considered of no clinical significance except for gastrointestinal hemorrhage and hypokalemia.

CONCLUSIONS

To anticipate complete quiescence of chronic active rheumatic fever by treatment with cortisone or corticotropin (ACTH) is speculative. From the data accumulated to date certain direct beneficial results can be attributed to adrenocortical therapy in the severely ill child with chronically active rheumatic fever. At times total quiescence may be achieved. Commoner is a disappearance of the manifestations of congestive heart failure despite a persistence of a degree of activity of the disease. In some children with severe disease the prolonged administration of large doses may be lifesaving.

Case Reports

CHROMOBACTERIAL INFECTION IN MAN

RUSSEL H. PATTERSON Jr.
GEORGE B. BANISTER, M.D.
AND
VERNON KNIGHT, M.D.
NEW YORK

THE GENUS Chromobacterium is made up of Gram-negative, aerobic, pigment-producing, bacilliform bacteria. Species differentiation depends partly upon the color of the pigment produced and partly on the growth and biochemical characteristics of the organism.[1] The strains of any given species vary considerably among themselves; hence attempts at precise classification are often unsatisfactory. A useful classification, however, is that of Topley and Wilson.[2]

Human disease caused by these bacteria is rather rare, and only a few cases have been reported.[3] Urinary tract infection has been noted to occur with some regularity, and the chromobacteria have less frequently been implicated as etiological agents in serious systemic infection. Of the reported cases, only in those of Wheat and his associates[4] has the role of specific antimicrobial therapy been studied. In their patients such therapy was found to be ineffective, and the bacteria were resistant to antimicrobial drugs in vitro. Recently we observed a case of infection with Chromobacterium prodigiosum in which the disease process could not be controlled despite an in vitro sensitivity of the organism to the agents employed in treatment. A description of this patient's course forms the basis of the present report.

REPORT OF CASE

The patient (66171-51) was a 63-year-old white male baker whose complaints on admission were hematemesis, melena, and weakness. Six years previously he had undergone subtotal gastrectomy for recurrent hemorrhage from a duodenal ulcer. After this operation he had persistence of epigastric pain and at least one episode of severe bleeding. In an effort to control these symptoms, a subdiaphragmatic vagotomy was performed four years prior to the present admission. He then remained asymptomatic until three months before admission, when he had a return of epigastric pain. Four days prior to admission he began to vomit large amounts of a dark brown material and to pass tarry stools.

Physical examination on admission revealed a well-nourished man with a moist, pale skin who appeared acutely ill and quite apprehensive. He had a moderate amount of upper abdominal

From the Cornell Medical and Surgical Divisions, Bellevue Hospital.

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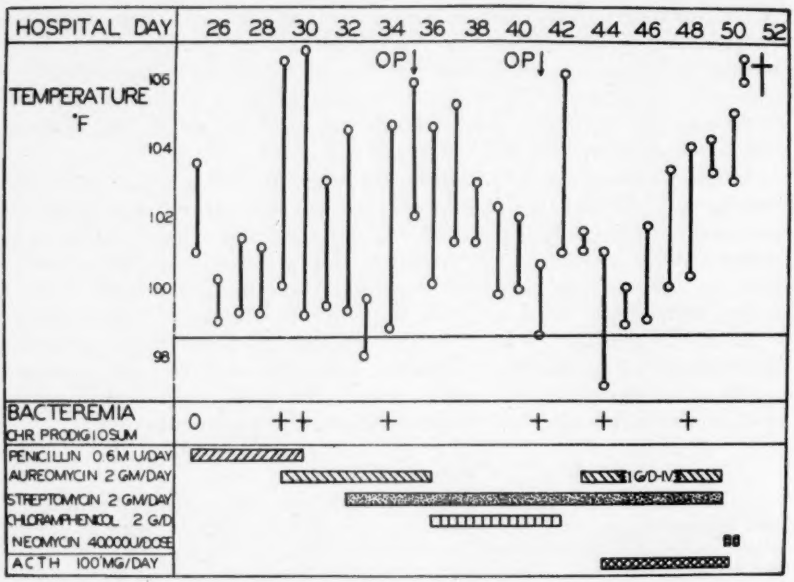
1. Hefferan, M.: A Comparative and Experimental Study of Bacilli Producing Red Pigment, Zentralbl. Bakt. (Abt. 2) **11**:311, 397, 456, and 520, 1903-1904.

2 Topley, W. W. G., and Wilson, G. S.: Principles of Bacteriology and Immunity, Ed. 3, revised by G. S. Wilson and A. A. Miles, Baltimore, Williams & Wilkins Company, 1946, pp. 631-641.

3. Infection Due to Chromobacteria, editorial, J. A. M. A. **148**:56, 1952.

4. Wheat, R. P.; Zuckerman, A., and Rantz, L. A.: Infection Due to Chromobacteria: Report of 11 Cases, A. M. A. Arch. Int. Med. **88**:461-466, 1951.

muscle spasm with some deep tenderness. Bowel sounds were easily audible with the stethoscope. His hemoglobin concentration was 2.8 gm. per 100 ml., the hematocrit reading, 12%, and the red blood cell count, 900,000 per cubic millimeter. The patient was put to bed, given sedatives as necessary, administered 300,000 units of procaine penicillin intramuscularly twice daily, and transfused by means of indwelling polyethylene venous cannulae. A working diagnosis of bleeding marginal ulcer was made. In view of his critical condition and because a third operative attempt to control hemorrhage would undoubtedly be a very serious procedure, conservative management was adopted. His course was one of intermittent low fever until 17 days after admission when, while receiving a blood transfusion, he had a chill and a temperature elevation to 105 F. This febrile episode and a similar one on his 25th hospital day were both treated with a total of 4 to 6 gm. of aureomycin in divided doses to supplement the penicillin therapy. Blood cultures on both occasions were sterile. He continued to show signs of gastrointestinal hemorrhage, but



Fatal course of Chr. prodigiosum infection with bacteremia in 63-year-old man, despite intensive antimicrobial therapy with agents active in vitro. Illness complicated by continued bleeding from jejunal ulcer, gastrojejunocolic fistula, and probable local peritonitis.

clinically appeared to be much improved since admission. On his 29th hospital day, he once again experienced a chill and his temperature rose to 106.2 F. Blood cultures at this time revealed a heavy growth of Chr. prodigiosum (see figure). At this time penicillin therapy was discontinued, and treatment with aureomycin was begun in a divided daily oral dosage of 2 gm. On the 32d hospital day streptomycin, 2 gm. per day intramuscularly, was added to the regimen. Despite this combined therapy blood cultures continued to be positive for Chr. prodigiosum. The patient's condition became worse, and gastrointestinal hemorrhage continued, as did a steady temperature elevation to 101 F. with frequent rises to 105 F. Finally, there was the vomiting of what appeared to be feces. It was now fairly clear that the patient had a gastrojejunocolic fistula. Accordingly, on the 35th hospital day, abdominal exploration was carried out, the presence of such a fistula confirmed, and a proximal colostomy formed. Postoperatively he appeared improved, but as the fever continued unabated, a change was made from aureomycin

and streptomycin to chloramphenicol and streptomycin in an empiric effort to find effective antimicrobial therapy. His fever lessened, but at the same time severe gastrointestinal hemorrhage resumed after having stopped for three days following establishment of the colostomy. On the 41st hospital day he was again subjected to operation in an attempt to control this hemorrhage.

At operation the viscera were found to be densely bound by adhesions. A large amount of fibrous tissue along the gastrocolic omentum and in the lesser peritoneal sac suggested that there had been a local peritonitis, perhaps following perforation of the marginal ulcer. As the afferent loop of jejunum to the gastrojejunostomy was too short to permit a block resection of the fistulous tract, the old anastomosis was taken down, the defects in the jejunum and the transverse colon were closed, and three-fourths of the remaining stomach was resected. Postoperatively, corticotropin (ACTH) was given for six days, and initially the patient appeared to improve with this therapy. As he could no longer take oral medication because of intubation, aureomycin was given intravenously in place of chloramphenicol. On the 46th hospital day, four days after operation, he began to show signs of pneumonia on the right side, and, in addition, sclericterus appeared. Treatment with neomycin on the 50th day was of no avail, and he died on his 51st hospital day. Permission for autopsy was not granted.

TABLE 1.—*Bacteriologic Characteristics of Chromobacterium from Present Case*

Milk coagulated	Yes
Hydrogen sulfide produced	Yes
Nitrate reduced	Yes
Voges-Proskauer reaction	Yes
Methyl red test	No
Indole test	No
Gelatin liquefied	Yes
Acid produced from:	
Lactose	Yes
Maltose	Yes
Mannitol	Yes
Glucose	Yes
Gas produced from:	
Lactose	No
Maltose	No
Mannitol	No
Glucose	Small amount

The final diagnoses were (1) septicemia due to Chr. prodigiosum, (2) bronchopneumonia, (3) gastrojejunocolic fistula secondary to a jejunal (marginal) ulcer, with hemorrhage (an index of the severity of the blood loss is reflected in the fact that he received 30.5 liters of blood during his hospital stay).

Bacteriologic Studies.—The last six consecutive blood cultures taken during the interval from the 29th to the 48th hospital day yielded Chr. prodigiosum. Urine cultures and cultures of the colostomy discharge on several occasions failed to reveal this organism. The bacterial species isolated was a Gram-negative, nonsporing, nonmotile rod, varying from 1 to 2 μ in length, and about 0.5 μ in diameter. Colonies at room temperature after 18 hours on blood agar were shiny, elevated, and about 1 mm. in diameter. They had a pink center and a gray-white periphery. In the part of the plate where growth was heaviest, the closely grouped colonies were orange. At seven days the colonies were raised and shiny with serrated edges, pink centers, and a gray-white periphery. They were brick red in the heavy clumps. Some cultures showed pseudopod formation, and others were hemolytic on blood agar, though most were not. In broth at 37 C. there was a dense growth in 18 hours with a red deposit on the glass at the broth surface. After two weeks all cultures had a strong odor similar to that of trimethylamine. On blood agar after initial isolation at 37 C. the predominant color was orange at 18 hours, turning to red at 36 hours, and was finally purple in two weeks. Subcultures at 37 C. were purple at 18 hours, but with repeated transfer at 37 C. pigment was no longer produced. The pigment was soluble in ether, chloroform, ethanol, and acetone, but not in water. A summary of the important biochemical characteristics of this strain is presented in Table 1.

The organism described above [5] closely resembled Chr. prodigiosum (Topley and Wilson [2]) and Serratia plymuthicum (Bergey [6]). The principal characteristics of S. plymuthicum are encompassed in the description of Chr. prodigiosum (synonym, Serratia marcescens) by Topley and Wilson, who do not describe a separate species conforming to the characteristics of S. plymuthicum. Most authors in writing of human infections with aerobic, nonsporing, red-pigment-producing, Gram-negative bacilli have employed the Topley and Wilson nomenclature. That precedent is, therefore, followed in the present report.

Drug-Susceptibility Tests.—In vitro drug-susceptibility tests were performed on this organism, and it may be seen (Table 2) that the first isolate was very sensitive to streptomycin (less than 1 γ per milliliter), moderately sensitive to the broad-spectrum agents, aureomycin, chloramphenicol, and terramycin (16 to 20 γ per milliliter), and quite resistant to penicillin (greater than 500 units per milliliter). After two weeks of therapy with streptomycin, however, resistance of the organism to this drug increased to 8 γ per milliliter. Interestingly enough, the bacteria recovered on the last blood culture were very highly susceptible to neomycin (less than 1 unit per milliliter).

COMMENT

In contrast to the uniform resistance in vitro of the 11 strains from cases studied by Wheat and his associates,[4] the organism from the present case was moderately to highly sensitive to the agents employed in therapy. Failure of therapy in such a situation leads to the suspicion that other factors limiting therapeutic effectiveness

TABLE 2.—*Susceptibility to Antimicrobial Agents**

Drug	34th Day	48th Day
Streptomycin	< 1	8
Streptomycin	1	8
Aureomycin	16	16
Chloramphenicol	20	..
Terramycin	20	..
Penicillin	500 units	..
Neomycin	..	< 1 unit

* Minimal inhibitory concentration in micrograms or units per cubic milliliter.

are present. Localized infections, such as abscesses, peritonitis, or endocarditis, often provide explanations, and, although no cultures were obtained from the site of penetration of the stomal ulcer, the gross observations at operation left little doubt that an infection existed there. With due consideration of the effect of this probable local infection, in addition to the continued massive blood loss, gastrojejunocolic fistula, and resulting serious deterioration in the patient's general condition, failure to respond to specific and potentially effective therapy is not surprising.

The present case is one more example of the seriousness of generalized infection with the chromobacteria, and, although such cases are few at present, cognizance must be taken of the possible influence of antimicrobial therapy in the selection of these unusual organisms, as has been emphasized by Wheat and his associates.[4] The present patient received penicillin and aureomycin before infection with Chromobacterium developed, and this therapy could reasonably have played a role in selection of the infecting agent.

5. Dr. Martha Ward, Special Bacteriology Laboratories, United States Public Health Service, Chamblee, Ga., assisted in identification of the organism.

6. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, ed. 6, Baltimore, Williams & Wilkins Company, 1948, pp. 481-482.

In addition to the red pigment produced by Chr. prodigiosum, violet and yellow pigments are produced by related species. All three groups have been implicated as causes of human infection. The clinical manifestations have varied widely, and for that reason it is of interest to summarize briefly reported human cases of infection with these organisms. Descriptions of the cases are presented below and in Table 3.

Chromobacterium Violaceum (Bacillus Violaceus).—Human infection with Chr. violaceum may be acute or chronic, but in any case it has usually terminated in death. An example of the acute course is the case of a 21-year-old man, reported on by Schattenberg and Harris,[7] who had an infected foot wound with subsequent marked inguinal adenitis. He died after a febrile course five days following admis-

TABLE 3.—*Summary of Data on Cases of Chromobacterial Infection*

Author	Organism	Presenting Complaints	Course
Woodward & Clark [14]	B. prodigiosus	24-year-old man with chronic cough and red, foul-smelling sputum	Repeated isolation of organism; symptoms cleared over 8 wk. with vaccine treatment
Altoff & others [15]	B. prodigiosus	In pure culture in sputum of a pneumonia patient	Not given
Paine [16]	S. marcescens	4 men exposed to aerosol of S. marcescens	Malaise, fever, and headache soon after exposure, subsiding for the most part in 24 hr.; probably toxic reaction rather than infection
Aronson & Alderman [12]	S. marcescens	21-year-old man had meningitis after lumbar puncture to evaluate known nervous system syphilis	Apparently well in 2 wk.; spinal fluid had 2,100 cells, elevated protein, and normal sugar
Wheat & others [4]	S. marcescens	11 urinary tract infections, with 1 transient bacteremia and 1 fatal bacterial endocarditis	1 man had septic fever with persistent bacteremia and died on the 21st day with jaundice; autopsy showed tricuspid endocarditis, liver damage, necrotic lung areas, and focal inflammatory areas in kidney
Patterson & others	Chr. prodigiosum	63-year-old man with long ulcer history and recent massive bleeding	Development of gastrojejunocolic fistula, with high fever, persistent bacteremia, bleeding, jaundice, and death
Schattenberg & Harris [7]	B. violaceus	21-year-old man with foot infection, inguinal adenitis, and fever	Died in circulatory collapse with icterus and hemoptysis 5 days after admission; autopsy showed many small abscesses in lungs, liver, and spleen
Soule [9]	B. violaceus	15-year-old girl with cervical adenitis and negative tuberculin reaction	9 months' course; clinical and gross pathological diagnosis, tuberculosis; but B. violaceus only organism isolated at autopsy
Black & Shahan [8]	B. violaceus	6-year-old boy with inguinal adenopathy, fever, and multiple anthrax-like skin lesions	Healed in 2 mo.; 13 mo. later reappeared with cervical adenitis and skin lesions; died 2 mo. later; no autopsy
Schütz & Laun [11]	Yellow pigment	Young man with recurrent abscesses	Isolated Chromobacterium from shoulder abscess on one occasion; died after 3-yr. course
Pangalos [10]	Yellow pigment	Woman had fever 5 days after curettage	Positive blood culture on 7th day; 4-week nonfatal course with low fever

sion to the hospital with terminal pyrexia, circulatory collapse, icterus, and hemoptysis. Autopsy showed yellow focal necrotic areas, varying from 1 to 5 mm. in diameter, in the lungs, liver, and spleen.

In contrast, Black and Shahan [8] reported the case of a 6-year-old boy who had a more chronic course. He had fever and inguinal adenopathy two or three days after wading in a pool of rain water. Skin lesions appeared over his arms and trunk,

7. Schattenberg, H. J., and Harris, W. H.: A Definite and Unique Occurrence of Rapidly Fatal Infection Caused by Bacillus Violaceus Manilae, J. A. M. A. **117**:2069-2070, 1941. Schattenberg, H. J.: Experimental Studies upon B. Violaceus, Isolated from a Fulminating Fatal Human Infection, Proc. Soc. Exper. Biol. & Med. **45**:829-831, 1940.

8. Black, M. E., and Shahan, J.: Bacillus Violaceus Infection in a Human Being, J. A. M. A. **110**:1270-1271, 1938; cited by Soule, M. H.: A Study of 2 Strains of B. Violaceus Isolated from Human Beings, Am. J. Path. **15**:592, 1939.

varying from ½ by 1 in. (1.3 by 2.5 cm.) in diameter to twice that size. Each had a dark mahogany eschar, with a pustular area of distinct violet surrounding it. B. violaceus was isolated from these lesions. Local treatment of the skin lesions was unsatisfactory, but the patient seemed to improve after two small blood transfusions. Two months after the onset of the illness, with a course marked by a remittent fever, the temperature reaching as high as 106.4 F., the patient was discharged apparently cured. Thirteen months later, however, he reappeared, prostrated, febrile, and with severe cervical adenitis. The adenitis subsided, and his body became covered with lesions, varying from minute vesicles to large, gangrenous areas. A short time later he died, approximately 15 months after first being observed. In this case B. violaceus was the only organism isolated.

A somewhat similar case was that of Soule,[9] in which a 15-year-old girl presented cervical lymphadenopathy which was diagnosed by biopsy as mixed tuberculous and pyogenic lymphadenitis, although tubercle bacilli were never found by culture. There was no evidence of tuberculosis elsewhere in the body, and the reaction to the tuberculin test was negative. The adenitis improved in association with radiation therapy, but the patient's condition became worse, and she died after nine months. At autopsy the diagnosis, on gross examination, was tuberculosis of the left lung base and multiple abscesses of the diaphragm, liver, spleen, and lung. Much to the surprise of all concerned, B. violaceus was the only organism isolated from the lesions. The characteristics of this organism were compared with those of the stock recovered from the 6-year-old boy (see above) and were found to be similar.

Chromobacterium Aquatile.—Infections with bacteria producing a yellow pigment, of which Chr. aquatile is the type species, are not frequently described in the literature. Pangalos [10] reported on a woman who exhibited a remittent fever five days following uterine curettage. On the seventh day a motile, Gram-negative bacterium was isolated from the blood which produced a brick-yellow pigment after three or four days' growth. The woman had a febrile course with a maximum temperature elevation to 39 C. (102.2 F.) in the second week. She was apparently well within four weeks. No specific therapy was described in the report.

A yellow-pigment-producing Gram-negative bacillus was isolated on one occasion from a man, described by Schütz and Laun,[11] who had a two-year fatal course marked by recurrent abscesses involving especially his extremities, face, and skull. Late in the course this organism was recovered once in pure culture from a shoulder abscess, and subsequent treatment with autogenous vaccine did not alter the progress of the disease. In addition, hemolytic streptococci and staphylococci were frequently isolated from these abscesses.

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9. Soule, M. H.: A Study of 2 Strains of B. Violaceus Isolated from Human Beings, Am. J. Path. **15**:592, 1939.

10. Pangalos, G.: Sur un bacille chromogène isolé par hémoculture, Compt. rend. Soc. biol. **100**:1097-1098, 1929.

11. Schütz, F., and Laun, H.: Über einen seltenen Bakterienbefund im menschlichen Abszesseiter, Zentralbl. Bakt. (Abt. 1) **129**:124-132, 1933.

Chr. Prodigiosum (S. Marcescens; Bacillus Prodigiosus).—Infections with Chr. prodigiosum have typically involved a specific organ system and may resolve with a clinical cure or, on the other hand, may progress to an overwhelming, fatal infection.

Aronson and Alderman [12] have reported a case of meningitis with this organism. It occurred in a 21-year-old man after a lumbar puncture carried out to evaluate known central nervous system syphilis. He first showed signs of a "cold" and a cough, soon followed by chills, fever, vomiting, and nuchal rigidity. Lumbar puncture revealed 2,100 cells per cubic millimeter, 92% of which were polymorphonuclear leucocytes. The protein was elevated, and the sugar was 50 mg. per 100 cc. The white blood cell count was 11,400 per cubic millimeter. The next day there were 1,700 cells, the protein was elevated, and the sugar was 92 mg. While Chr. prodigiosum was isolated by culture of the spinal fluid, no bacteria was seen in the centrifuged sediment. Eleven days later the cell count had fallen to 25, with 70% lymphocytes. The patient went on to recovery, though no mention was made of specific therapy.

Urinary tract infection is probably the commonest disease process caused by Chr. prodigiosum. Draper,[13] at Bellevue Hospital, New York, studied 100 cases of urinary tract infection and found that 2 were due to chromogenic bacteria. Wheat and associates [14] recently reported 11 such cases, all following some form of genitourinary manipulation. In contrast, this source could not be implicated in our case, as these bacteria were never recovered from the patient's urine. Two of the patients of Wheat and co-workers displayed a bacteremia, one transient and the other continuous and resulting in death. The latter patient's course was one of daily temperature elevations, with chills and profuse sweating. Jaundice developed on the 20th day, and he died on the 21st day. Autopsy showed bacterial endocarditis of the tricuspid valve, extensive liver damage, necrosis and hemorrhage in the lungs, and small inflammatory lesions in the kidneys. The strain involved in this case was highly resistant to antimicrobial agents; however, during therapy with chloramphenicol the colony counts of the patient's blood fell from 200 to 5 to 10 per cubic centimeter.

Chr. prodigiosum may be present in both naturally occurring and artificially induced infections of the respiratory tract. Woodward and Clark [14] reported the case of a 24-year-old man who complained of a chronic cough of three years' duration. The sputum appeared to be blood-stained and had a foul odor. On repeated culture, colonies with the characteristics of B. prodigiosus were isolated. He was treated with autogenous vaccine for eight weeks, when the color disappeared from his sputum. A brief note in the French literature by Aïtoff and colleagues [15] mentioned a case of pneumonia in which a sputum culture grew only this organism.

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12. Aronson, J., and Alderman, I.: The Occurrence and Bacteriologic Characteristics of Serratia Marcescens from a Case of Meningitis, J. Bact. **46**:261-267, 1943.

13. Draper, J.: Unpublished data.

14. Woodward, H. M. M., and Clark, K. B.: A Case of Infection in Man by the Bacterium Prodigiosum, Lancet **1**:314, 1913.

15. Aïtoff, M.; Dion, M., and Dobkevitch, H.: Bacillus prodigiosus pathogène pour les animaux: Endotoxine et réaction de Shwartzman, Compt. rend. Soc. biol. **123**:375-376, 1936.

Paine [16] detailed an experiment in which four men were exposed to an aerosol containing a concentration of 2,000,000 S. marcescens organisms per cubic foot for two and one-half hours. From two and one-half to four hours later, all complained of smarting of the eyes, malaise, chilliness, aches in the head, back, and legs, and cough with green sputum. Three had chills and fever, but the acute phase lasted only 6 to 11 hours. In two there was fever at 24 hours, but after four days all were asymptomatic. The early onset and short duration of symptoms in these cases suggested that the etiological mechanism was the action of some toxic product of S. marcescens (Chr. prodigiosum) rather than actual invasion by the bacteria.

From the foregoing reports it may be observed that infection with the chromobacteria can be an acute fulminating process or a long-continued relapsing illness. In any event, the prognosis is poor for patients in whom the infection is generalized, since seven of nine patients described above with bacteremia or disseminated abscesses died. The disease produced by strains which elaborate different-colored pigments did not appear to vary greatly in severity, and, in fact, many of the reported cases resembled those of other Gram-negative bacillary infections caused by such organisms as Pseudomonas aeruginosa or Proteus vulgaris (Bacillus proteus).

SUMMARY

A case of a human infection with Chromobacterium prodigiosum associated with bacteremia is reported in which there was a fatal outcome, despite intensive antimicrobial therapy.

A review of the literature shows that systemic infections with chromobacteria are rare, that they have a high case fatality rate, and that treatment with antimicrobial drugs in cases in which they were available did little to alter the outcome.

16. Paine, T.: Illness in Man Following Inhalation of Serratia Marcescens, J. Infect. Dis. **79**:226-232, 1946.

FAMILIAL CHRONIC LYMPHATIC LEUKEMIA

EMMETT B. REILLY, M.D.
SAMUEL I. RAPAPORT, M.D.
NORMAN W. KARR, M.D.
HAROLD MILLS, M.D.
AND
GURTH E. CARPENTER, M.D.
LONG BEACH, CALIF.

THIS REPORT is on three brothers with chronic lymphocytic leukemia. It is of interest not only because of the rarity of the condition but because the evaluation of heredity in the causation of this disease in man depends upon such families being on record.

Reviews of familial leukemia were published by Ardashnikov in 1937 [1] and by Videbaek in 1947.[2] The latter compiled, from the literature and his own observations, 82 authenticated cases of leukemia in 37 families. These included four families in which three persons were afflicted and two families with four leukemic members. In this group the disease was found in two or more generations, except for a family originally described by Hornbaker,[3] in which two sisters had chronic lymphogenous leukemia and a third sister had chronic myelogenous leukemia. Recently, Anderson [4] reported on a remarkable family in which five siblings were afflicted with leukemia. It is believed that the cases described in this report are the third recorded instance of leukemia occurring in more than two siblings.

REPORT OF CASES

SIBLING 1.—P. R. died in 1948 at the age of 36. He was not examined by us. He had been carefully studied at the Mayo Clinic, Rochester, Minn., four years before his death. At that time he gave a history of peripheral adenopathy noted since the age of 22. He had an enlarged spleen and axillary and inguinal adenopathy. His white blood cell count was 30,000 per cubic millimeter, with 85.5% lymphocytes. The blood smear was described as typical of chronic lymphatic leukemia. He received a course of x-ray therapy. He returned to work until two weeks prior to his death. The immediate cause of death is unknown to us.

From the Department of Pathology and Internal Medicine, Veterans Administration Hospital.

Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Ardashnikov, S. N.: Genetics of Leukemia in Man, J. Hyg. **37**:286-302 (April) 1937.

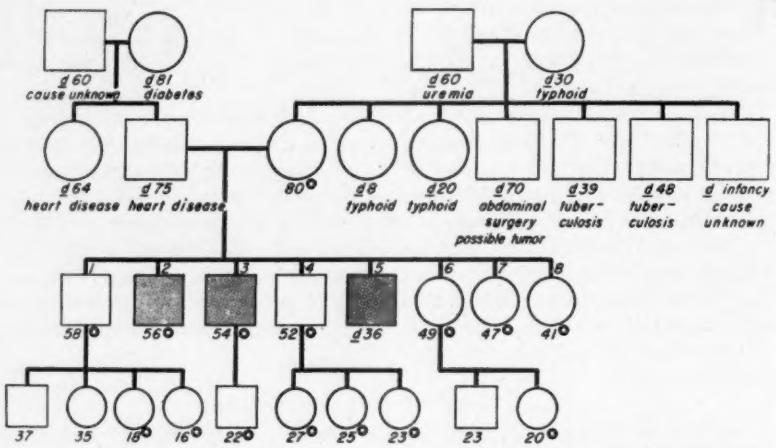
2. Videbaek, A.: Familial Leukemia: Preliminary Report, Acta med. scandinav. **127**:26-52, 1947.

3. Hornbaker, J. H.: Chronic Leukemia in 3 Sisters, Am. J. M. Sc. **203**:322-325 (March) 1942.

4. Anderson, R. C.: Familial Leukemia: A Report of Leukemia in 5 Siblings, with a Brief Review of the Genetic Aspects of this Disease, A. M. A. Am. J. Dis. Child. **81**:313-322 (March) 1951.

Sibling 2.—D. E. R., aged 54, has been followed in this hospital since September, 1948, when a routine chest roentgenogram revealed a right hilar mass. Examination at that time showed generalized lymphadenopathy. The spleen has never been palpable. White blood cell counts have varied from 20,000 to 140,000 per cubic millimeter, with 70 to 90% small mature lymphocytes. The hemoglobin concentration was varied from 10.5 to 18 gm. per 100 cc., and the thrombocyte (platelet) count from 120,000 to 340,000 per cubic millimeter. Two bone marrow aspirations have shown 52 and 54% lymphocytes in the sternal marrow. Biopsies of two axillary lymph nodes have revealed infiltrations characteristic of lymphocytic leukemia. Treatment with corticotropin (ACTH) produced a subsidence of the peripheral and hilar adenopathy, which recurred, however, after seven months and responded only partially to re-treatment. In addition to lymphocytic leukemia, the patient suffers from episodes of bronchial asthma and acute bronchitis superimposed upon chronic bronchitis.

Sibling 3.—R. V. R., aged 56, entered this hospital in August, 1950, because of fever, coughing, and shortness of breath for four days. He had experienced attacks of asthma and acute bronchitis for more than 30 years. Physical findings at that time were those of asthma,



Pedigree of the R. family. Circled stars indicate members personally examined; *d* indicates deceased; shaded boxes represent leukemic members of the family; numbers indicate age.

emphysema, and acute bronchopneumonia. There was no peripheral or hilar adenopathy and no splenic enlargement. However, a blood count showed 53,350 white blood cells per cubic millimeter, with 77% small mature lymphocytes. Since then generalized peripheral lymphadenopathy, hilar adenopathy, splenomegaly, and hepatomegaly have gradually developed. The patient's blood count now shows 12.5 gm. of hemoglobin per 100 cc. and 120,000 white blood cells per cubic millimeter, with 92% lymphocytes. Treatment with radioactive phosphorus (P^{32}) has been instituted.

FAMILY DATA

The pedigree of the R. family is outlined in the figure. The causes of death in Generations I and II are known by history only, and therefore may not be completely reliable. The circled stars denote those persons examined by us. The brothers with chronic lymphocytic leukemia are indicated by the shaded symbols. The other members of the family who were examined were free of findings suggestive of leukemia. They have normal blood counts and blood smears. One sister suffers from severe rheumatoid arthritis and atopic dermatitis.

There have been no consanguineous marriages in this family. All the children of Generation III were nursed by their mother. No significant environmental factor has been unearthed. However, it is noted that each of the three affected brothers, but none of the other siblings, received a course of therapy with autogenous vaccine prepared by a local laboratory. This was several years before the discovery of the leukemia.

COMMENT

This family is believed to be another illustration of the role of genetic predisposition in the genesis of leukemia in man, a fact long suspected and clearly documented by the studies of Videbaek.[2] The mode of genetic transmission remains to be clarified. Because most of the families Videbaek studied revealed leukemia in two or more generations, he felt that irregular dominance was the most likely manner of inheritance. However, families such as the present one, in which the disease is confined to several siblings of a single generation, may be explained best by an uncommon recessive gene of high penetrance.

Other points in this family report worthy of note are the following: All of the leukemic members were males. All had lymphocytic leukemia. The age of onset of peripheral adenopathy in one sibling was 22 years, which is unusual since chronic lymphocytic leukemia is generally discovered after the age of 50.

Dr. B. F. Hall, of the Mayo Clinic, Rochester, Minn., provided a summary of the clinical findings on Sibling P. R.

USE OF QUINIDINE SULFATE AND OF PROCAINE AMIDE IN A PATIENT WITH PAROXYSMAL VENTRICULAR TACHYCARDIA

ROBERT A. CHAPMAN, M.D.
CHICAGO

VENTRICULAR arrhythmias have recently received increased attention owing to their susceptibility to treatment by procaine amide.[1] The usual report has been that in ventricular tachycardia procaine amide has been used successfully after the failure of relatively large doses of quinidine, with either oral or intravenous use of the latter drug. Claggett[2] has recently compiled results of the intravenous use of quinidine from 15 authors on 62 cases of ventricular tachycardia and found that in 42 of these cases there was reversion to sinus rhythm with the use of quinidine in intervals ranging from 30 minutes to 21 days from the beginning of treatment. Claggett has a comprehensive bibliography on the oral and intravenous use of quinidine appended to his report.

The present report concerns a recurrent form of ventricular tachycardia which could not be controlled adequately with recommended oral doses of procaine amide, although it was temporarily controlled with procaine amide given intravenously. The patient has responded well to low dosage of quinidine sulfate orally.

REPORT OF CASE

V. N., a 54-year-old Italian man, came to the Research and Educational Clinic on Feb. 24, 1951, complaining of recurrent "dizzy spells" for about eight weeks. These occurred daily, and as many as 8 or 10 attacks would take place in one day. One month previous to this first visit he had quit working at molding plastics because of sharp pain across his chest, which, however, ceased on his lying down for a few minutes. He had recently noted dyspnea on slight exertion.

The patient's wife stated that he had become much slower mentally and less stable emotionally recently. Her description of the patient's "dizzy spells" was as follows: He complained of a peculiar sensation "in his stomach," then he stiffened and his eyes rolled upward, and he would fall and have jerking, convulsive movements. He was able to get up within a minute. At no time did he lose bowel or urinary bladder control.

Clinical Instructor in Medicine, Illinois Research and Educational Hospitals.

From the Department of Medicine, University of Illinois College of Medicine.

1. Burstein, C. L.: Treatment of Acute Arrhythmias During Anesthesia by Intravenous Procaine, Anesthesiology **7**:113, 1945. Miller, H.; Nathanson, M. H., and Griffith, C. C.: Procaine Amide in Cardiac Arrhythmias, J. A. M. A. **146**:1004, 1951. Garlett, E. L.; Berry, K. W.; Bellet, S., and Gefter, W. I.: Preliminary Observations on the Use of Procaine Amide on Ventricular Arrhythmias, J. Philadelphia Gen. Hosp. **2**:30, 1951. Mark, L. C.; Berlin, I.; Kayden, H. J.; Rovenstine, E. A.; Steele, J. M., and Brodie, B. B.: The Action of Procaine Amide on Ventricular Arrhythmias, J. Pharmacol. & Exper. Therap. **98**:21, 1950. Kinsman, J. M.; Clay, H. L.; Coe, W. S., and Best, M. M.: Procaine Amide (Pronestyl) in the Treatment of Disorders of Cardiac Rhythm, J. Kentucky M. A. **48**:509, 1950. Irwin, C. W., and Cutts, F. B.: Ventricular Tachycardia: Report of a Case in Which "Pronestyl" was Effectively Used After Failure of Quinidine, J. A. M. A. **146**:1282, 1951.

2. Claggett, A. H.: Intravenous Use of Quinidine, with Particular Reference to Ventricular Tachycardia, Am. J. M. Sc. **220**:381, 1950.

Physical examination revealed a normally developed, well-nourished man, who appeared to be somewhat older than his stated age. The blood pressure was 139/90. Funduscopic examination revealed increased light reflex of the arteries and an arteriovenous ratio of 2:7. The retinal veins appeared larger than normal. There was no carotid sinus hypersensitivity or marked variation in blood pressure on change from lying to standing. The physical examination

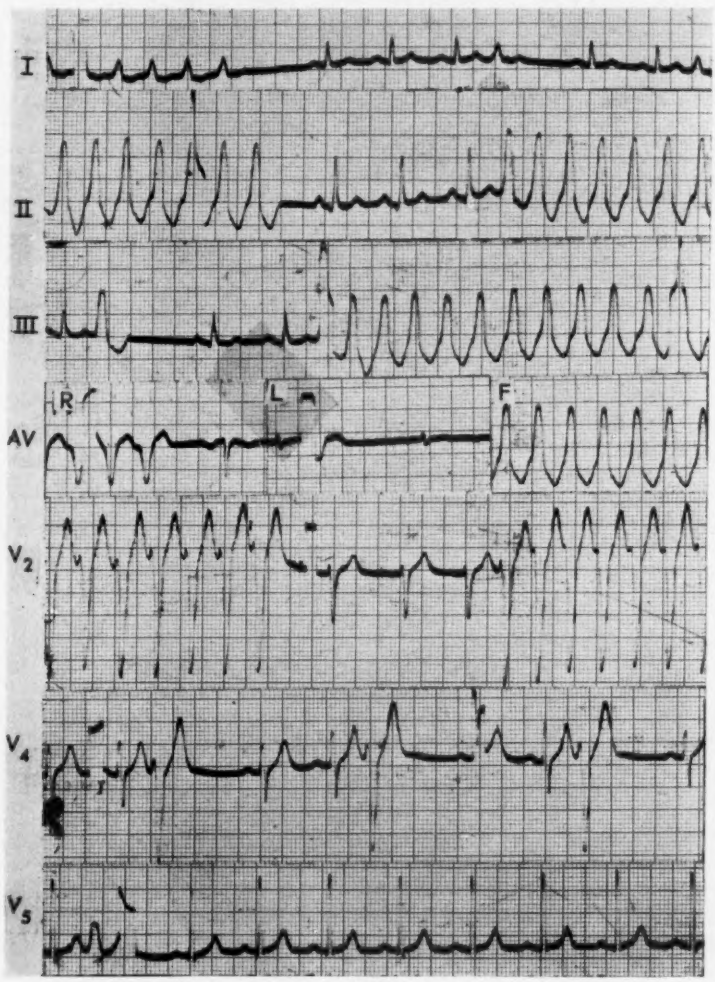


Fig. 1.—Tracing taken March 28, 1951, showing series of ventricular beats at a rate of 220 per minute, alternating with normal sinus beats at rate of 92 per minute. Pulsus trigeminus is present in Lead V_4. Normal sinus rhythm is present in Lead V_5.

of the chest revealed emphysema. There were no rales. The heart sounds were distant; the rate was 88, and the sounds were regular except for an occasional premature beat. No cardiac thrills or murmurs were present. The radial pulses were not readily compressible. Pedal pulses were present bilaterally.

Neurological examination showed nothing abnormal except an equivocal left facial nerve weakness.

Results of urinalysis, hematological examination of the peripheral blood, serologic tests, and blood nonprotein nitrogen and serum protein determinations were all normal or within normal

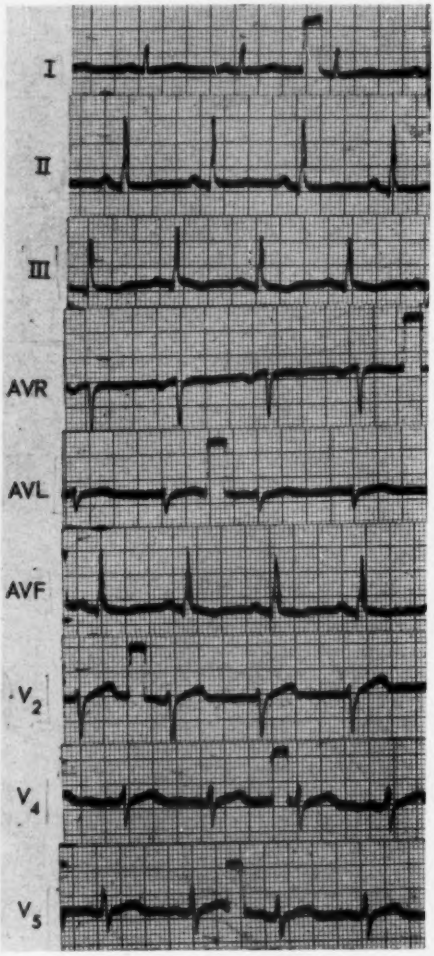


Fig. 2.—Representative tracing taken April 5, 1951, while patient received 0.5 gm. of procaine amide every six hours. Low T waves are present in Leads I, II, AVR, AVL, and AVF. Patient had received digitalis continually until seven days previous to this tracing.

limits. Roentgenographic examinations of the chest and the skull revealed no significant abnormalities, with the exception of a suspected bronchiectasis at the right cardiophrenic angle.

Thirty-three days later the patient came to the clinic. While he was waiting on a bench in the hall he collapsed and had a convulsion. He was taken to the electrocardiography laboratory, and a tracing revealed sequences of 4 to 15 ventricular beats at a rate of 220 per minute, alter-

nating with normal sinus rhythm at a rate of 92 per minute (Fig. 1). The patient was admitted to the hospital. His physical and laboratory findings had not changed.

At the time of admission the patient was given 0.25 gm. of procaine amide orally every four hours. On the first morning after admission he stated he had one of his episodes of "feeling like the heart stopped," but the sensation disappeared spontaneously within less than a minute.

The dose of procaine amide was raised gradually to 0.75 gm. every four hours, and repeated electrocardiograms revealed no significant changes in the P or T waves or in the QRS complexes or Q-T interval. His pulse was checked every two hours during this hospital admission of 14 days, and only an occasional extrasystole was noted.

The patient was discharged with instructions to take a regular dose of 0.5 gm. of procaine amide every six hours. Eight days after discharge, he reported that he had had two or three attacks a day, and his dosage interval was shortened to four hours. On the 11th day after discharge from the hospital an electroencephalogram was made. He had not had any medicine for 16 hours and had been instructed to stay awake until midnight the night before the test. In the morning while waiting for the test, he had an episode of syncope from which he recovered in a few minutes. The electroencephalogram, taken during sleep induced with secobarbital (seconal®) sodium revealed no focal abnormality or seizure discharges.

The next clinic visit was 30 days later. The patient had noted that his trouser waistband was becoming tighter, and he was unable to eat as large a meal as formerly without abdominal discomfort and fulness. He had gained 5 lb. (2.3 kg.) in the past month with a reduced food

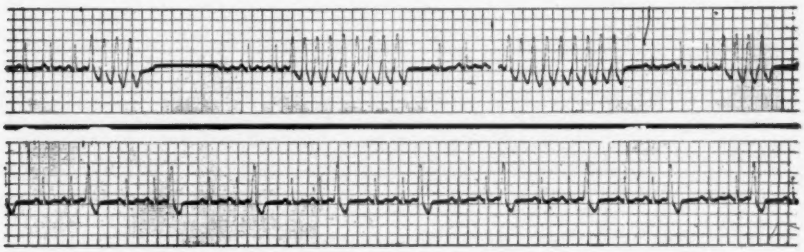


Fig. 3.—Tracing taken May 23, 1951, second day of second hospital admission. Top strip, Lead II before treatment with procaine amide intravenously. Bottom strip, Lead II after treatment with 0.4 gm. of procaine amide given in four minutes. Pulsus trigeminus.

intake; also attacks of "the heart stopping" occurred whenever the patient got out of bed, and consequently he spent almost all day in bed, leaving his home only for medical appointments. On physical examination, he appeared to have basilar rales and there was shifting dulness newly present in both flanks. It was decided to readmit him to the hospital for closer observation.

Clinical and Electrocardiographic Observations with Procaine Amide Given Intravenously and Quinidine Sulfate Given Orally.—On the second hospital day at 10:15 a. m., the patient was taken from his room to the examining room and, after returning to bed, complained he was "having spells" of his "heart stopping." An electrocardiogram was taken immediately and showed series of three normal sinus complexes alternated with series of 7 to 10 ventricular beats at a rate of 220; occasionally there was a single ventricular premature systole instead of a series of ventricular beats interposed between the groups of three normal sinus complexes (Fig. 3, top strip).

At 10:30 to 10:35 the patient received 0.5 gm. of procaine amide in 5 cc. solution (solution "pronestyl" hydrochloride). After injection of 4 cc. of the solution, the patient's rhythm changed to a pulsus trigeminus (Fig. 3, bottom strip). At 10:39 he had a normal sinus rhythm with an occasional premature ventricular beat. At 10:44 the patient had 10 ventricular premature beats in one minute. At 10:55 he had a pulsus quadrigeminus; at 11 a. m. he had one ventricular premature beat in 30 seconds, and at 11:05 he had three ventricular premature systoles in 30 seconds.

Under supervision he did 10 sit-ups in 30 seconds and had 12 premature ventricular systoles in one minute. They occurred singly after every fifth normal sinus complex. At 11:20 the

patient had a normal sinus rhythm. At 11:30 six ventricular premature systoles in one minute were noted. At 12:30, there appeared five ventricular premature systoles and one six-cycle bout of ventricular tachycardia at a rate of 220 per minute.

At 2 p. m., immediately after walking to the bathroom and passing stool, the patient had continual recurrent bouts of ventricular tachycardia ranging from 4 to 11 complexes each. The systolic blood pressure was 136 mm. of mercury during the presence of normal complexes and was unobtainable during the bouts of ventricular tachycardia. These groups of ventricular beats numbered 15 in one minute; in addition there were 7 single premature beats. The basic arrhythmia consisted of two normal complexes followed by either a single ventricular premature beat or 4 to 11 ventricular complexes.

At 2:10 the patient received 0.4 gm. of quinidine sulfate orally, accompanied with a drink of cold water. A normal sinus rhythm was noted five minutes later. This change was attributed to the stimulus of the cold water, and the next day the patient had a similar response after drinking cold water alone during a recurrence of ventricular tachycardia.

Electrocardiograms before and after 10 sit-up exercises were taken at 30-minute intervals for two hours, and then at hourly intervals until 9 p. m. At 5:40 he was noted to have two

Fig. 4.—Tracing taken May 24, 1951, third day of second hospital admission. Top strip, spontaneous recurrence of short series of ventricular tachycardia 8 hours 45 minutes after administration of 0.2 gm. of quinidine sulfate orally. Middle strip, change to pulsus quadrigeminus immediately after drinking cold water. Bottom strip, reversion to short series of ventricular tachycardia upon exercise.

ventricular premature systoles in one minute, but there was also the same frequency of ventricular premature systoles following an exercise test of 10 sit-ups in 30 seconds. Otherwise there was no disturbance of the normal sinus rhythm.

In order to estimate the length of action of a 0.2-gm. dose of quinidine, the patient was given the dose at midnight, and no further quinidine was given until the patient had a spontaneous recurrence of the short volleys of ventricular tachycardia at 8:40 a. m. (Fig. 4, top strip). This reverted to a pulsus quadrigeminus after he drank cold water alone (Fig. 4, middle strip), but the tachycardia appeared again about 30 seconds after an exercise test (Fig. 4, lower strip). The patient was given 0.2 gm. of quinidine sulfate orally. It was found that he had an occasional premature ventricular systole at rest at 9:35, which was 45 minutes after the oral dose of quinidine. The arrhythmia progressed to frequent short volleys of ventricular tachycardia after two of three standard exercise tests. However, three exercise tests were given at each of the following times: 9:45, 10:30, 10:55, and 11:55 a. m. and 12:30 and 4:05 p. m., and there was no disturbance of the sinus rhythm. The patient had a spontaneous recurrence at 5:45, about 8 hours 45 minutes after oral administration of quinidine. This interval agreed quite closely with the previous test in length of action of the quinidine.

The patient was discharged from the hospital to receive 0.2 gm. of quinidine orally every six hours. His first recurrence on this regimen was a single attack lasting two hours about two months following his second hospital admission. He had no further attacks of the arrhythmia for two months; at that time he had pulsus quadrigeminus, and his quinidine dosage was doubled.

The only other medications and regimen prescribed have been ammonium chloride for an expectorant, diuretics by the intramuscular route, and a diet with no added salt. The patient has responded well to very occasional use of the mercurials. He returned to work one month after the increase of quinidine dosage and had a normal sinus rhythm one month later (10 months after his first clinic visit).

The ventricular tachycardia originated from a single ventricular focus. There was no evidence of recent myocardial infarction indicated by electrocardiography.

SUMMARY

A patient with frequent attacks of continual short volleys of ventricular tachycardia of 4 to 15 ventricular complexes at a time at a rate of 220 per minute was unsuccessfully treated with 0.5 gm. of procaine amide hydrochloride orally every four hours. A trial of 0.5 gm. of procaine amide in solution given by the intravenous route was found to be effective for less than four hours. Subsequently he was satisfactorily controlled for five months with 0.2 gm. of quinidine sulfate every six hours.

Gelvin-Haughey Clinic, Concordia, Kan.

Progress in Internal Medicine

ALLERGY—CORTICOTROPIN AND CORTISONE

A Review of the Literature from September, 1950, to January, 1952

RICHARD R. EVANS, M.D.
AND
FRANCIS M. RACKEMANN, M.D.
BOSTON

THE REVIEW of the literature on allergy from August, 1948, to September, 1950, which was published in April, 1951, by one of us,[1] discussed the nature and the actions of corticotropin (ACTH) and cortisone in their broad aspects. Since then, there have been many new studies, for the remarkable effects of these drugs have made them the object of major interest in the clinic as well as in the laboratory. Let us look first at the results of laboratory studies.

LABORATORY STUDIES

The Effect of Corticotropin and Cortisone on Immune Processes

In regard to the effect of corticotropin and cortisone on immune processes, the possibilities are several: The adrenal cortical hormone may act by inhibiting the formation of antibodies, or perhaps by inhibiting the action of those already formed. It may prevent the union of antibody with antigen; it may alter the chemical effector which results from that union, or, finally, it may modify the response of the tissues to the effector. There are studies which throw light on each of these possibilities.

Since Leger, Leith, and Rose [2] first demonstrated the inability of corticotropin to prevent anaphylaxis in guinea pigs, further studies have extended and confirmed their observation. Malkiel [3] treated guinea pigs with corticotropin or cortisone before and after sensitization with horse serum, but he did not prevent fatal anaphylactic shock when the animals were challenged. Dews and Code,[4] using egg white, also failed. Landau, Nelson, and Gay [5] gave corticotropin or cortisone at various intervals prior to the challenging dose, but without effect on the shock. On the other hand, Humphrey [6] reported that cortisone gave definite protection.

From the Allergy Clinic, Massachusetts General Hospital.

Dr. Evans is Clinical Assistant in Medicine, and Dr. Rackemann is a member of the Board of Consultation, Massachusetts General Hospital.

1. Rackemann, F. M.: Allergy—Histamine and ACTH: A Review of the Literature from August 1948 to September 1950, A. M. A. Arch. Int. Med. **87**:598, 1951.

2. Leger, J.; Leith, W., and Rose, B.: Effect of Adrenocorticotrophic Hormone on Anaphylaxis in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **69**:465, 1948.

3. Malkiel, S.: The Influence of ACTH and Cortisone on Histamine and Anaphylactic Shock in the Guinea Pig, J. Immunol. **66**:379, 1951.

4. Dews, P. B., and Code, C. F.: Effect of Cortisone and ACTH During Sensitization on Eosinophils and Anaphylaxis in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **77**:141, 1951.

5. Landau, S. W.; Nelson, W. A., and Gay, L. N.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Histamine Reactions and Anaphylactic Reactions in Guinea Pigs, Bull. Johns Hopkins Hosp. **88**:395, 1951.

6. Humphrey, J. H.: Effect of Cortisone upon Some Experimental Hypersensitivity Reactions, Brit. J. Exper. Path. **32**:274, 1951.

Passive sensitization is not affected by corticotropin or cortisone. Malkiel [8] found that neither corticotropin nor cortisone could protect guinea pigs passively sensitized with rabbit anti-egg-white serum when challenged with a dose of egg white. Arbesman, Neter, and Bertram [7] observed that corticotropin and cortisone were ineffective in preventing both active and passive anaphylaxis in guinea pigs. In addition, they studied reversed Forssman anaphylaxis. Guinea pigs which were given intracardiac injections of anti-sheep-red-cells rabbit serum were not protected by cortisone against subsequent death, but use of corticotropin did lower the death rate somewhat. In another experiment, rabbit anti-guinea-pig serum was injected into the hearts of normal guinea pigs, and shock took place (reversed anaphylaxis). Both corticotropin and cortisone gave some protection against this reaction.

Using the Dale bath, Landau, Nelson and Gay [5] tested intestinal muscle strips from two actively sensitized guinea pigs which had been treated with corticotropin 30 to 90 minutes before they were killed. These muscle strips showed contractions similar to those of strips from the controls. Intestinal strips from two animals treated for four days with corticotropin and then passively sensitized also reacted with vigorous contractions. The hormone had no effect.

In these experiments, doses of the hormones ranged from the equivalent of those used in the treatment of patients to doses 10 times as great.

As a whole, these results show that neither corticotropin nor cortisone can prevent the development of active hypersensitivity in guinea pigs. The hormones have no effect on the fixation of sensitizing antibody to the shock organ as in passive anaphylaxis, or on the antigen-antibody reaction as manifested by anaphylactic shock.

Histamine

Although histamine has not yet been proved to be the specific effector substance in anaphylaxis and allergy, its actions are allied, and studies of them are important.

Malkiel [8] could not prevent death from histamine shock in guinea pigs by pretreatment with single doses of cortisone. Landau and his associates [5] could not prevent the fatal shock even with large and repeated doses of corticotropin or cortisone. When in another experiment histamine was added to the Dale bath, intestinal strips from corticotropin-treated guinea pigs contracted as vigorously as did strips from untreated controls.

In the clinic, Curry [8] and Segal and his co-workers [9] measured the changes in pulmonary function in man during asthmatic attacks induced by histamine or by acetylcholine and then studied the protection afforded by various drugs. Thus, epinephrine, ephedrine, aminophylline, and the antihistamines were shown to be protective. With the same technique, Curry, Roche, Doolin, and Kyle [10] studied corticotropin. They found that when corticotropin was given in varying doses before the tests no significant protection could be demonstrated.

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7. Arbesman, C. E.; Neter, E., and Bertram, L. F.: The Effect of ACTH and Cortisone on Certain Immunologic Mechanisms Including Reversed Anaphylaxis, J. Allergy **22**:340, 1951.

8. Curry, J.: The Effect of Antihistamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects, J. Clin. Invest. **25**:792, 1946.

9. Herschfus, J. A.; Rubitsky, H. J.; Beakey, J. F.; Bresnick, E.; Levinson, L., and Segal, M. S.: Evaluation of Therapeutic Substances Employed for the Relief of Bronchial Asthma: A Review, Internat. Arch. Allergy & Appl. Immunol. **2**:97, 1951.

10. Curry, J. J.; Roche, R. J.; Doolin, P. D., and Kyle, L. H.: Experimental Study of ACTH in Induced Histamine Asthma, abstracted, Am. J. Med. **9**:394, 1950.

Rose and his associates [11] made some interesting metabolic studies. They reported that histamine excretion in the urine of asthmatic persons was generally much greater than that in normal persons. After treatment with corticotropin, the histamine excretion in the urine generally increased, although not always. At the same time, the urinary histidine increased considerably, approaching levels noted during pregnancy. These values returned to pretreatment levels when administration of corticotropin was discontinued. The significance of these changes is not clear, however.

They also found that patients with intrinsic asthma usually excreted small amounts of glucocorticoids and 17-ketosteroids, while patients with extrinsic asthma excreted normal amounts. Both groups showed a rise in excretion of these two substances during treatment with corticotropin.

From the results of all these different experiments, one can say that corticotropin and cortisone do not have any "antihistamine" effect.

Skin Tests and Reagins

Skin tests of the immediate wheal and erythema type demonstrate the presence of antibodies in the skin cells. With them go antibodies, called reagins, in the circulating blood which can transfer the local tissue sensitiveness to the skin of a normal recipient, as von Prausnitz and Küstner [12] first showed. When corticotropin and cortisone have such a dramatic effect upon symptoms, one might expect that the drugs would affect skin-test reactions and reagins also. Carey, Harvey, Howard, and Winkenwerder [13] noted a significant reduction in skin-test reactions in four of five ragweed-sensitive patients during corticotropin treatment, but no diminution in serum reagins.

Most investigators, however, have not found any significant reduction in skin reactivity in patients with hay fever or extrinsic asthma during treatment with corticotropin or cortisone. Passive transfer tests by most workers likewise showed the titers of serum reagins to be unchanged. Skin-test reactions to dilutions of histamine are unaffected by corticotropin and cortisone administration.

When the shock organ was tested directly, the results were more variable. Feinberg, Dannenberg, and Malkiel [14] observed conjunctival and nasal reactions in 13 patients to be unchanged by corticotropin or cortisone treatment. One patient did show diminished skin, eye, and nasal reactions, and another exhibited a

11. Rose, B.; Pare, J. A. P.; Pump, K. K.; Stanford, R. L.; MacKenzie, K. R., and Venning, E. H.: Observations on the Metabolic Changes Resulting from the Administration of ACTH to Patients with Asthma and Allied Conditions, in Proceedings of the Second Clinical ACTH Conference, Vol. I: Research, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, p. 519.

12. von Prausnitz, C., and Küstner, H.: Studien über die Überempfindlichkeit, Centralbl. Bakt. **86**:160, 1921.

13. Carey, R. A.; Harvey, A. M.; Howard, J. E., and Winkenwerder, W. L.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on the Course of Chronic Bronchial Asthma, Bull. Johns Hopkins Hosp. **87**:387, 1950.

14. Feinberg, S. M.; Dannenberg, T. B., and Malkiel, S.: ACTH and Cortisone in Allergic Manifestations: Therapeutic Results and Studies on Immunological and Tissue Reactivity, J. Allergy **22**:195, 1951.

decreased nasal reaction, but no change in the skin or eye reaction. Loveless [15] found a patient whose eye reaction was decreased while the skin reaction remained unchanged after corticotropin administration.

Circulating Antibodies

The effects of corticotropin and cortisone on circulating antibodies have been studied. Many different methods have been employed, and the results have varied to an interesting extent. Mirick [16] immunized 46 patients with a mixture of Pneumococcus polysaccharides and measured the antibodies by means of the protective technique in mice. One group was treated with corticotropin, a second, with cortisone, and a third was left as controls. Antibodies were formed equally well in all three groups. Positive Francis reactions (immediate reactions to the intradermal injection of the polysaccharide) were observed in 8 of 11 treated patients and in 7 of 9 controls. The corticotropin administered had made no change. Agglutinins to Salmonella typhosa H in a titer of 1 : 10 or greater happened to be found in five of these same patients. After corticotropin therapy the titer fell in two of them. Mirick also determined the isohemagglutinin titers to the O, A, or B blood groups in 11 patients. During treatment with corticotropin the titers rose in 5 of the 11.

Carey, Harvey, Howard, and Wagley [17] studied a patient having syphilis and paroxysmal cold hemoglobinuria with cold urticaria. When this patient was treated with corticotropin and then exposed to cold, urticaria did not develop, but the cold hemolysin, cold agglutinin, complement, and reagin titers were unchanged.

Dameshek, Rosenthal, and Schwartz [18] found that corticotropin treatment produced dramatic benefit in eight patients who had acquired hemolytic anemia, whether the disease was secondary to lymphoma or "idiopathic." During treatment, there was almost complete remission of the hemolytic process. The "warm" hemagglutinins disappeared, and the "cold" hemagglutinin titer decreased markedly, while the reaction to the Coombs test (with rabbit antihuman globulin) remained positive. When treatment was stopped, hemolysis returned. Unger [19] has reported a similar result in one case.

Arbesman, Neter, and Bertram [7] treated a group of rabbits with corticotropin during sensitization with sheep cells and found no effect on the agglutinin titers. Mitchell and associates [20] observed no significant changes in S. typhosa agglutinins

15. Loveless, M. H.: The Influence of ACTH on the Sensitizing and Immunizing Antibodies of Inhalant Allergy, Bull. New York Acad. Med. **27**:495, 1951.

16. Mirick, G. S.: The Effects of ACTH and Cortisone on Antibodies in Human Beings, Bull. Johns Hopkins Hosp. **88**:332, 1951.

17. Carey, R. A.; Harvey, A. M.; Howard, J. E., and Wagley, P. F.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Drug Hypersensitivity Reactions, Bull. Johns Hopkins Hosp. **87**:354, 1950.

18. Dameshek, W.; Rosenthal, M. C., and Schwartz, L. I.: The Treatment of Acquired Hemolytic Anemia with Adrenocorticotrophic Hormone (ACTH), New England J. Med. **244**:117, 1951.

19. Unger, L. J.: The Effect of ACTH in Acquired Hemolytic Anemia, Am. J. Clin. Path. **21**:456, 1951.

20. Mitchell, R. B.; Fulton, J. D.; Talbot, J. M., and Kimball, A. W.: Effect of Adrenal Cortical Steroids on Circulating Antibodies in X-Radiated Animals, Texas Rep. Biol. & Med. **9**:576, 1951.

when immunized rabbits were treated with adrenal cortex extract. Osgood and Favour [21] gave corticotropin for 16 days to 23 guinea pigs, previously sensitized to tubercle bacilli, and noted no gross changes in the circulating complement-fixing antibody levels.

Experimental Hypersensitivity

The fascinating experiments of Rich on periarteritis nodosa need no recounting. His work has been extended. Berthrong, Rich, and Griffith [22] sensitized rabbits with large single doses of horse serum. To 39 of them they gave corticotropin in 15 to 18 daily doses, beginning on the day of the horse-serum injection. To another group of 20 animals, Rich, Berthrong, and Bennett [23] gave cortisone in similar fashion. There was an equal number of controls. Of the 59 control animals, 51 had lesions. Periarteritis was observed in 45; endocarditis, in 21. Among the treated animals, only 14 of the 59 had lesions. There was periarteritis in only 12 and endocarditis in only 7. In these experiments corticotropin and cortisone were equally effective. An interesting addition is the observation that skin tests with horse serum made on the 12th day gave positive reactions in both the treated and the control animals. Precipitating antibody, measured by the antigen-dilution method, was present in all sera, although the treated rabbits had a slightly lower titer. No parallel between the antibody titer and the development of visceral lesions was found.

Additional lesions not found in the corticotropin-treated or control groups developed in the cortisone-treated rabbits. The kidneys showed dilated capillary loops in the glomeruli, with focal necrosis of cells. Large hyaline masses appeared in the tufts, similar to the changes seen in diabetes and in disseminated lupus erythematosus. Another observation by Rich, Cochran, and McGoon [24] was that lipemia developed in the cortisone-treated animals. Fat droplets were observed in the serum, as well as in the liver cells.

One can say that the presence of positive skin-test reactions indicates that corticotropin and cortisone neither prevent the development of hypersensitivity nor inhibit the capacity of the skin to react, even though they do inhibit the development of arterial lesions (see also Bennett, Berthrong, and Rich [25]).

Arbesman, Neter, and Bertram [7] also noted that the precipitin titers of rabbits sensitized to guinea-pig serum were unchanged by treatment with corticotropin, when measured by the antigen-dilution method.

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21. Osgood, C. K., and Favour, C. B.: The Effect of Adrenocorticotropic Hormone on Inflammation Due to Tuberculin Hypersensitivity and Turpentine and on Circulating Antibody Levels, J. Exper. Med. **94**:415, 1951.

22. Berthrong, M.; Rich, A. R., and Griffith, P. C.: A Study of the Effect of Adrenocorticotropic Hormone (ACTH) upon the Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **86**:131, 1950.

23. Rich, A. R.; Berthrong, M., and Bennnett, I. L., Jr.: The Effect of Cortisone upon the Experimental Cardiovascular and Renal Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **87**:549, 1950.

24. Rich, A. R.; Cochran, T. H., and McGoon, D. C.: Marked Lipemia Resulting from the Administration of Cortisone, Bull. Johns Hopkins Hosp. **88**:101, 1951.

25. Bennett, I. L., Jr.; Berthrong, M., and Rich, A. R.: A Further Study of the Effect of Adrenocorticotropic Hormone (ACTH) upon the Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **88**:197, 1951.

Seifter and his co-workers,[26] using a smaller number of rabbits sensitized like Rich's animals with a large single dose of horse serum, observed that cortisone prevented arteritis and carditis in eight of their nine animals, but that nephritis was not prevented. When horse serum was injected intradermally on the 14th day, five of seven rabbits had positive skin-test reactions. Antibody titers were not measured. Desoxycorticosterone acetate and "artisone" (21-acetoxypregnenolone) had no effect on the vascular lesions. Hyaluronidase, however, seemed to enhance arteritis and carditis, although glomerular nephritis was diminished. Rich's work seems to indicate that cortisone itself can cause glomerular lesions in rabbits, perhaps by its metabolic effect on fat.

In experiments of opposite types, Criep, Mayer, and Menchaca [27] removed the adrenal glands from a group of rabbits, maintained them on desoxycorticosterone acetate, and then sensitized them to horse serum essentially as did Rich. They noted the precipitin titers, as measured by the antibody-dilution technique, to be increased, the skin reactions to be more intense, and the vascular lesions to be more extensive, when compared with those of the controls.

The Arthus Phenomenon

The Arthus phenomenon, so closely concerned with circulating precipitating antibodies, provides another illustration of the effects of corticotropin and cortisone.

Tillotson [28] found that cortisone given to rabbits during sensitization with horse serum (but not after sensitization was established) inhibited both the Arthus reaction and the development of precipitating antibodies as measured by the antigen-dilution technique.

Bjørneboe, Fischel, and Stoerk [29] immunized rabbits with polyvalent Pneumococcus antigen given intravenously and measured the specific antibody nitrogen by a quantitative agglutination method. They reported that when corticotropin and cortisone were given during immunization and afterward there was a reduction in circulating antibody.

Pathologic changes characteristic of those observed after prolonged immunization occurred in all the control immunized animals. The spleen was enlarged and showed an increase in the number and size of large mononuclear cells in the pulp, with strikingly enlarged germinal centers in the Malpighian bodies. There was a dense infiltration of mononuclear cells, especially plasma cells, in the red pulp. The thymus showed a decrease of cortical tissue, with a relative increase of medullary tissue. The lymph nodes were enlarged. Quite different were the pathologic changes in the hormone-treated animals. In these the spleen showed moderate to marked atrophy of the Malpighian bodies, pigmentation of lymphocytes in the follicles, an absence of cellular infiltration of Billroth's cords, and a lack of plasma-cell accumulation.

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26. Seifter, J.; Ehrich, W. E.; Begany, A. J., and Warren, G. H.: Effects of Cortisone, Hyaluronidase, Desoxycorticosterone and Artisone on Experimental Serum Disease in Rabbits, Proc. Soc. Exper. Biol. & Med. **75**:337, 1950.

27. Criep, L. H.; Mayer, L. D., and Menchaca, O. E. L.: The Effect of Adrenalectomy on Experimental Hypersensitiveness, J. Allergy **22**:314, 1951.

28. Tillotson, F. W.: Effect of Cortisone on the Arthus Phenomenon as Related to the Time of Sensitization, A. M. A. Arch. Path. **52**:119, 1951.

29. Bjørneboe, M.; Fischel, E. E., and Stoerck, H. C.: The Effect of Cortisone and Adrenocorticotrophic Hormone on the Concentration of Circulating Antibody, J. Exper. Med. **93**:37, 1951.

The reduction in circulating antibody by hormone treatment was the interesting observation. Whether this reduction was due to inhibition of antibody formation or to increased breakdown of antibody protein was the next question. Bjørneboe and his associates [30] determined the rate of disappearance of anti-pneumococcus-antibody globulin which was injected intravenously into cortisone-treated and untreated rabbits and found it to be identical in the two groups. Cortisone does not promote the breakdown of injected antibody.

Germuth, Oyama, and Ottinger [31] reported an important series of carefully controlled experiments on the Arthus phenomenon. They injected crystalline egg albumin intradermally each day for 18 days into 24 rabbits, and then measured precipitating antibodies by a quantitative immunochemical technique. Eight of the 24 animals received at the same time corticotropin, and 8 others received cortisone. All the eight controls displayed large Arthus reactions by the 13th day, and most of them had at least 200 γ per milliliter of antibody nitrogen in the serum by the 18th day. The corticotropin-treated rabbits showed some inhibition of the Arthus reaction, and their antibody levels averaged only 50% of that of the controls. None of the cortisone-treated group showed more than slight skin reaction, and none had hemorrhagic lesions; none of this group had more than 12 γ per milliliter of antibody nitrogen, and 4 had no detectable antibody nitrogen. The smaller Arthus reactions could be correlated with the lower levels of precipitating antibody.

Subsequent studies showed that a level of about 40 γ of antibody nitrogen per milliliter is necessary to elicit a maximum Arthus reaction. Cortisone given in a daily dose of 2 mg. per kilogram of body weight during sensitization regularly reduced the level of antibody nitrogen to well below 40 γ per milliliter. Corticotropin suppressed the circulating antibody level, but not below this critical value. When cortisone was given after sensitization was established, it inhibited the Arthus reaction, provided that the duration of treatment was sufficient to reduce the antibody to a low enough level. The inhibitory effect of cortisone was temporary. When administration of the hormone was discontinued, a gradual rise in the circulating antibody and, correspondingly, an increase in the severity of the reaction occurred.

At the end of these experiments, passive sensitization of guinea pigs with serum from the three groups of rabbits was attempted. When the guinea pigs were challenged with egg albumin, those receiving serum from the control and corticotropin-treated rabbits showed passive Arthus reactions, but those receiving serum from the cortisone-treated group, which contained a low level of precipitins, did not. These various experiments show again that the relation between the Arthus reaction and the antibody level is direct.

Skin reactivity was studied also, by the same authors, to rule out a nonspecific tissue effect. On the 18th day of the original experiment, each rabbit received rabbit antipneumococcal serum intradermally. Thirty minutes later, each site was injected with the specific Pneumococcus polysaccharide antigen. All rabbits, control and treated alike, produced a similar positive local passive Arthus reaction. The skin was able to react in normal fashion, despite the treatment with cortisone. When

30. Fischel, E. E.; Stoerck, H. C., and Bjørneboe, M.: Failure of Cortisone to Affect Rate of Disappearance of Antibody Protein, Proc. Soc. Exper. Biol. & Med. **77**:111, 1951.

31. Germuth, F. G., Jr.; Oyama, J., and Ottinger, B.: The Mechanism of Action of 17-Hydroxy-11-Dehydrocorticosterone (Compound E) and of the Adrenocorticotropic Hormone in Experimental Hypersensitivity in Rabbits, J. Exper. Med. **94**:139, 1951.

another group of rabbits was treated with cortisone for four days, and then passively sensitized with anti-bovine-albumin-rabbit antibody, the Arthus reaction following challenge was positive. Again, the skin reactivity was not altered by treatment. The conclusion seems justified thereby that the inhibiting effect of cortisone on the Arthus phenomenon in rabbits is due to the specific inhibition of precipitating antibody.

These studies on the effect of corticotropin and cortisone on circulating antibodies thus show different results. Some of these differences may depend upon the species of animal studied or upon the techniques used for measuring antibody levels, but perhaps the type of antibody measured is more important.

Antibody Types.—Antibodies are complex entities. Different types have been demonstrated in different conditions by highly technical methods. Marrack's review [32] described four types. The first is the complete precipitating and agglutinating antibody, which has a high affinity for antigen. The second is the incomplete nonprecipitating antibody, sometimes called "univalent," with an intermediate affinity for antigen, which Heidelberger and Kendall [33] described in 1935. They found that when one adds the optimal amount of antigen to a given quantity of antibody all at once, precipitation is complete: The filtrate will not react with additional amounts of antigen. When, however, the antigen is added in small increments until no more precipitate is formed, and then the several precipitates are collected and added, one finds that the amount of antibody removed is less than that removed before. The balance represents "non-precipitating antibody."

A third type is the incomplete inhibiting, or "blocking," antibody, which in vitro inhibits precipitation or agglutination by the complete antibody. The demonstration of this depends upon the use of plasma or albumin instead of saline solution as the diluent for the antigen. A fourth type is the incomplete antibody with a low affinity for antigen that can be detected only by special techniques, such as the Coombs test.

The role of these different types of antibodies in allergic reactions is not yet understood. Marrack [32] discussed reagins—the special antibodies of clinical allergy—and reviewed the evidence which indicates that reagins may be antibodies of the incomplete "univalent" type. Benacerraf and Kabat [34] have demonstrated in the guinea pig that nonprecipitating "univalent" antibody can produce passive anaphylactic sensitivity, but it cannot induce the passive Arthus reaction. This suggests that anaphylaxis and the Arthus phenomenon, in guinea pigs, are mediated by different antibodies. In another experiment Benacerraf and Kabat found that the passive Arthus reaction in guinea pigs can be elicited immediately after the intravenous injection of precipitating antibody; that no latent period is really necessary. On the other hand, the fact that the passing of time after the intravenous injection increases the ability to effect passive anaphylaxis makes it hard to exclude the importance of fixed antibody in passive anaphylaxis.

32. Marrack, J. R.: The Biological Significance of Complete and Incomplete Antibodies, Internat. Arch. Allergy & Appl. Immunol. **2**:264, 1951.

33. Heidelberger, M., and Kendall, F. E.: Quantitative Theory of Precipitin Reaction: Reaction Between Crystalline Egg Albumin and Its Homologous Antibody, J. Exper. Med. **62**:697, 1935.

34. Benacerraf, B., and Kabat, E. A.: A Quantitative Study of the Arthus Phenomenon Induced Passively in the Guinea Pig, J. Immunol. **64**:1, 1950.

Since corticotropin and cortisone do not prevent anaphylaxis but can inhibit the Arthus phenomenon and lower the precipitating antibody, and since these reactions may be mediated by different types of antibodies, it is possible that the hormones have different actions on different antibodies. Moreover, they may have effects upon circulating antibodies different from those upon fixed-tissue antibodies. Corticotropin and cortisone may prove to be valuable tools in the further understanding of this problem.

The Effect of Corticotropin and Cortisone on Tissue Reactions of the Delayed, Inflammatory Tuberculin Type.—This effect is another problem. Here, the antibody is believed to be exclusively cellular.

Long and Favour [35] studied the intradermal responses to tuberculin and to a beta hemolytic Streptococcus vaccine in patients who were receiving corticotropin and cortisone. The reaction to the purified protein derivative was obliterated in 13, and the Streptococcus reaction was blocked in 19 of the 34 patients, but these two effects were not necessarily present in the same patient. The time of obliteration varied from 3 to 30 days and was modified by the initial degree of sensitivity, the dose of hormone, and the time. In those reactions not blocked entirely, there was a significant diminution of induration and erythema. Necrosis was the most readily altered phase. In some cases, a diminished or obliterated reaction lighted up again within 36 hours of discontinuance of the hormone treatment, even though the testing material had been dormant in the skin for more than one week. When the tests were older than three weeks, however, this "rebound" phenomenon did not occur. When patients were retested after treatment with either corticotropin or cortisone, positive reactions usually returned within 7 to 28 days. When 12 untreated control patients with rheumatoid arthritis were tested repeatedly, they showed a wide variation in induration and erythema from week to week. This is important, for the variation in reactivity makes the effect of cortisone not too easy to interpret.

Carey and his associates [13] also made intradermal tests with bacterial vaccines and observed positive delayed reactions in 11 patients. During corticotropin treatment a significant reduction in the size of the reaction occurred in 8 of the 11. These same 11 patients had positive reactions to old tuberculin, all of which were reduced during hormone treatment.

LeMaistre and co-workers [36] treated six patients who had advanced tuberculosis with corticotropin or cortisone. The skin hypersensitivity was reversed in three and in two of the three remained obliterated for three to four weeks after treatment was stopped.

Woods and Wood [37] studied the effect of corticotropin and cortisone on eye reactions to bacterial vaccines and also to tuberculous infections. When rabbits sensitized to Group A beta hemolytic streptococci by daily intradermal injections then received an injection of a small dose of streptococci in the anterior chamber, an iritis developed in each animal and lasted seven days. Corticotropin and cortisone

35. Long, J. B., and Favour, C. B.: The Ability of ACTH and Cortisone to Alter Delayed Type Bacterial Hypersensitivity, Bull. Johns Hopkins Hosp. **87**:186, 1950.

36. LeMaistre, C. H.; Tompsett, R.; Muschenheim, C.; Moore, J. A., and McDermott, W.: Effects of Adrenocorticotropic Hormone and Cortisone in Patients with Tuberculosis, J. Clin. Invest. **30**:445, 1951.

37. Woods, A. C., and Wood, R. M.: The Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:482, 1950.

blocked the reaction and also blocked the previously positive skin-test reactions. In another experiment the workers observed that the hormones could prevent the development of tuberculous iritis in rabbits. The skin-test reactions to tuberculin were markedly depressed at the same time. To study the specificity of this effect, they injected glycerin or jequirity into the eye and then showed that previous treatment with corticotropin or cortisone could block the inflammatory reaction.

Osgood and Favour [21] gave corticotropin in huge doses for 16 days to 23 tuberculin-sensitive guinea pigs and noted a significant reduction in the area of erythema and a striking diminution in the induration of the tuberculin reaction during treatment. All the animals showed a marked fall in lymphocytes and eosinophiles. Six rabbits received the same dose of corticotropin and then received intradermal injections of turpentine oil. Erythema and induration were suppressed, but the central necrosis was unchanged.

Derbes and his associates [38] found no diminution in the strongly positive tuberculin reaction of tuberculous guinea pigs when they were treated with 1 mg. of corticotropin or cortisone daily from the day prior to infection. When the dose of corticotropin was increased to 10 mg. a day for seven days, and that of cortisone to 20 mg. a day for three days, however, the tuberculin reaction then was modified but not abolished.

Sheldon, Cummings, and Evans [39] also noted that the tuberculin reaction in similarly infected guinea pigs was decreased by corticotropin or cortisone given in daily doses of 2 mg. for six days. Sections of the lesions showed a diminution in proliferation of fibroblasts and endothelium.

These several experiments indicate that the inhibiting effect of corticotropin and cortisone on the local tuberculin reaction and related tissue reaction may be a nonspecific action on the associated inflammation rather than upon the fixed tissue antibodies.

The Shwartzman Phenomenon.—The Shwartzman phenomenon is another example of altered tissue reactivity closely allied to allergy. When a bacterial filtrate is injected intradermally into rabbits, mild local inflammation develops. If, in 24 hours, the same or another bacterial filtrate or a nonspecific substance, even including starch, is injected intravenously, a severe hemorrhagic necrosis develops at the prepared skin site. Soffer and associates [40] demonstrated that corticotropin given prior to the preparatory injection had no effect on the phenomenon. When it was given prior to the intravenous, or provocative, injection, however, hemorrhagic necrosis was prevented. These results have been confirmed by Thomas and Mogabgab.[41] Again, the nonspecific effect of the hormones on inflammation is suggested.

38. Derbes, V. J.; Dent, J. H.; Weaver, N. K., and Vaughan, D. D.: Response of Tuberculin Skin Test to ACTH and Cortisone in Tuberculous Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **75**:423, 1950.

39. Sheldon, W. H.; Cummings, M. M., and Evans, L. D.: Failure of ACTH or Cortisone to Suppress Tuberculin Skin Reactions in Tuberculous Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **75**:616, 1950.

40. Soffer, L. J.; Shwartzman, G.; Schneierson, S. S., and Gabrilove, J. L.: Inhibition of the Shwartzman Phenomenon by Adrenocorticotropic Hormone (ACTH) from the Adenohypophysis, Science **111**:303, 1950.

41. Thomas, L., and Mogabgab, W. J.: Hemorrhagic Skin Lesions Produced by Intradermal Meningococcus Toxin in Rabbits Following Treatment with ACTH or Cortisone, Proc. Soc. Exper. Biol. & Med. **74**:829, 1950.

Vascular Reactions of Hypersensitivity.—These reactions have been studied in the living animal by Ebert and Wissler,[42] who used the rabbit-ear-chamber technique. A thin layer of vascularized tissue grows over a glass slide, which can then be illuminated to provide direct observation under high magnification. Furthermore, a given area can be marked, so that the same blood vessels can be observed from day to day or from week to week.

In their first experiment, they gave two injections of 10 ml. of horse serum per kilogram of body weight intravenously 18 to 20 days apart to a group of normal rabbits and followed the changes. After the first dose, they observed mild changes in the small venules in four to seven days. After the second injection, however, striking changes appeared immediately. There were localized constrictions and dilatations (changes in "tone") of the arterioles, focal endothelial swelling, and proliferation in both arterioles and vessels. Leucocytes adhered to the endothelial surfaces. Intravascular clumping of red blood cells ("sludging") and transient thrombocyte (platelet) and white blood cell thrombi were particularly prominent. These changes in the small blood vessels point to the fact that the vascular reaction occurring in anaphylaxis is widespread.

In their second and critical study, Ebert and Wissler [43] gave cortisone to sensitized rabbits at various intervals before the second, or shocking, dose of horse serum. They noted a marked reduction in both the vascular and the intravascular phenomena. In addition, they demonstrated that the effect of cortisone was temporary, for after the hormone treatment was stopped and horse serum was injected again the vascular changes were seen once more.

These studies show that cortisone has a pronounced inhibitory effect on reactions of small blood vessels. Whether this effect is specific for those vessels or nonspecific for the reaction as a whole is hard to say. The authors cited unpublished experiments which demonstrated a similar protective action of cortisone in preserving vascular integrity following trauma. These results would point to a nonspecific effect.

Ebert,[44] by this same technique, found that treatment with cortisone also provided a quantitative reduction in the inflammatory response to tuberculosis infection in tuberculin-sensitive rabbits.

Comment

This review brings out several interesting observations on corticotropin and cortisone, which together throw a little light on the mechanism of the allergic reaction. With the use of these new hormones, one can distinguish between an effect on antibody, which can be called "specific," and an effect on inflammation in general, which can be called "nonspecific." All authors do not agree that the ordinary

42. Ebert, R. H., and Wissler, R. W.: In Vivo Observations on the Vascular Reactions to Large Doses of Horse Serum Using the Rabbit Ear Chamber Technique, J. Lab. & Clin. Med. **38**:511, 1951.

43. Ebert, R. H., and Wissler, R. W.: In Vivo Observations of the Effects of Cortisone on the Vascular Reaction to Large Doses of Horse Serum Using the Rabbit Ear Chamber Technique, J. Lab. & Clin. Med. **38**:497, 1951.

44. Ebert, R. H.: In Vivo Observations on the Effect of Cortisone on Experimental Tuberculosis Using the Rabbit Ear Chamber Technique, in Transactions of the 47th Annual Meeting of the National Tuberculosis Association, 1951.

antibodies which confer immunity and which produce passive sensitization in animals are affected. They do agree, however, that the transfer of positive skin-test reactions in man ("reagins") is not affected by the hormones, and that skin-test reactions in clinical allergy are not affected. Direct tests to the eye or nose of sensitive subjects show changes with corticotropin or cortisone administration which are "variable." The passive Arthus reaction—in which the animal is prepared by large doses of antibody—is unaffected by previous treatment of the recipient animal with hormone, but the active Arthus reaction—in which the animal is actively sensitized by repeated doses of antigen—is suppressed considerably. Since Germuth and co-workers [31] found in their careful study of the Arthus reaction that the circulating antibody titer was reduced by cortisone, and since the Arthus reaction is reduced at the same time, one must conclude that the action concerns the antibodies and, therefore, is "specific." Whether there is also a nonspecific factor is not entirely clear.

Meantime, the physical chemists, beginning with Heidelberger and Kendall and continuing with Marrack and with Kabat, have been able to differentiate types of antibodies on the basis of their physical properties and then on the basis of their functions in immune reactions. The nonprecipitating or "univalent" antibody appears to have a special importance. It can sensitize to passive anaphylaxis, but it cannot sensitize to the passive Arthus reaction, and evidently the failure depends on qualitative rather than on quantitative factors. Incidentally, it is this nonprecipitating antibody which is coming to have some importance in hay fever. It is tempting to consider that corticotropin and cortisone have different effects in different situations, because these are produced by different types of antibody—but such an idea must remain speculative until much more fundamental work is done.

So far, the important action of the hormones is obvious; it is reduction of inflammation by a mechanism not yet known. This "nonspecific" effect explains the reduction of the tuberculin reaction in tuberculin-sensitive animals; it explains the inhibition of the Shwartzman phenomenon, and it explains the reduction of the vascular changes seen in Ebert and Wissler's rabbit ear chambers when the sensitized rabbits were shocked with horse serum.

The way in which corticotropin and cortisone exert their effects in allergic phenomena is better understood, even though what they really do is not yet known. What they do not do is quite clear; thus, the problem is far from solved. Let us see what these hormones do clinically.

CLINICAL STUDIES

Renold and colleagues,[45] from Thorn's clinic at the Peter Bent Brigham Hospital, Boston, recorded the effectiveness of corticotropin when given intravenously in stimulation of the adrenal cortex. They showed that 20 mg. given in a slow intravenous drip over eight hours produces maximum adrenal cortical stimulation, as measured by the fall in circulating eosinophiles and the rise in urinary 17-ketosteroids. They demonstrated that a larger dose gives no greater stimulation but that the longer duration of infusion will increase the adrenal response. Meantime, the intravenous method produces a more rapid effect; it requires only one-fifth to

45. Renold, A. E.; Forsham, P. H.; Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH: A Preliminary Report, New England J. Med. **244**:796, 1951.

one-tenth of the intramuscular dose. It saves material and expense; it is effective in an occasional case in which intramuscularly given corticotropin is not, presumably because of some tissue factor that prevents the hormone from reaching the circulation.

In another paper, these same investigators [46] compared the physiological and clinical effects of oral and intramuscular use of cortisone. Measured by the eosinophile response, the action of cortisone when given by mouth is more rapid, more marked, and of shorter duration than when the dose is given intramuscularly. The effectiveness of the total daily dose is similar whether cortisone is given orally at six-hour intervals or intramuscularly once a day. The rapidity of action makes the oral route preferable in acute diseases requiring immediate high levels of cortisone.

Corticotropin and Cortisone in Asthma

In the past year, numerous papers have described clinical studies and critical evaluations of the effects of corticotropin and cortisone in asthma. There is a remarkable uniformity of results.

Table 1.—*Corticotropin in Asthma*

Author	No. of Cases	Results			First Dose, Mg.	Days of Therapy	Relief	
		Complete	Moderate	Poor			Began, Days	Lasted, Days
Carey,[13] 1950	19	15	4	0	20-140	4-21	2-11	3-300 (av. 5)
McCombs,[52] 1950	23	20	2	1	60-200	5-22	1-4	3-135 (av. 37)
Segal,[47] 1950	27	18	7	2	160	3-14	....	Short
Cooke,[49] 1951	12	9	2	1	80-100	6-20	3-14	2-180
Feinberg,[14] 1951	14	6	3	5	80-160	6-15	1-2	2-165
Friedlaender,[50] 1951	10	6	2	2	100	6-16	....	7-42
Baldwin,[54] 1952	8	7	0	1	75-150	6-38	....	Few
Franklin,[48] 1952	16	8	6	2	80	....	1-5	1-60 (av. 4)
Total	129	89	26	14				
Per cent	100	69	20	11				

Tables 1 and 2 are compiled from the reports which present the larger series of cases. Most of the patients treated with these hormones have been in the older age group. Most of them had what we call "intrinsic asthma." All were refractory to ordinary treatment. They had been followed long enough to establish a base line of "chronicity." Many of them, and especially those in the earlier series, had serious asthma uncontrolled by hospital management. As the tables show, about 65% of the group have been completely relieved, at least for a time. Another 20% have become quite comfortable, needing only occasional supplementary medical treatment. The results are truly extraordinary.

The method of treatment has been essentially the same in all clinics. A large "suppressive" dose is given initially: 100 to 300 mg. a day of cortisone or 80 to 160 mg. a day of corticotropin. This dosage is maintained until improvement

46. Thorn, G. W.; Renold, A. E.; Wilson, D. L.; Frawley, T. F.; Jenkins, D.; Garcia-Reyes, J., and Forsham, P. H.: Clinical Studies on the Activity of Orally Administered Cortisone, New England J. Med. **245**:549, 1951.

occurs, usually within three to five days, and then the dosage is slowly decreased in stepwise fashion—the slower the better. Corticotropin was not used intravenously in the reports comprising Tables 1 and 2.

It will be noted that relief sometimes came slowly, requiring 6 to 14 days in some patients. This means that the failure of a patient to respond in three to four days is not an indication that the drug is ineffective. Either a greater dose or a longer course of treatment is necessary before deciding that the drug is useless in a particular case. In general, the severer the disease, the larger the dose that is necessary.

The duration of remissions is particularly interesting. Unfortunately, they are not long, but ranges are wide, as the tables show. All too often asthma returns within hours to days after the treatment is stopped. On the other hand, occasional remissions of up to five or six months are reported. With good control of asthma, the severely depleted patient may be able to regain weight, strength, and courage

TABLE 2.—*Cortisone in Asthma*

Author	No. of Cases	Results			First Dose, Mg.	Days of Therapy	Relief	
		Complete	Moderate	Poor			Began, Days	Lasted, Days
Carey,[18] 1950	5	1	4	0	200-300	8-11	6	.....
Cooke,[49] 1951	19	10	9	0	100	9-30	3-14	14-180
Feinberg,[14] 1951	7	1	2	4	200	7-28	1-2	2-30 (av. 12)
Friedlaender,[50] 1951	31	17	7	7	100-300	6-16	1-2	7-42
Schwartz,* 1951	22	17	0	5	200-300	1-45	1-3	14
Baldwin,[54] 1952	7	7	0	0	75-100	2-10	....	Few
Franklin,[48] 1952	25	19	6	0	100-300	....	1-5	1-60 (av. 8)
Total	116	72	28	16				
Per cent	100	62	24	14				

* J. A. M. A. 147:1734, 1951.

enough to carry on. Whereas in the past many patients have done well without hormones as soon as their general health improved the new treatment makes them turn the corner faster. One must observe that the duration of relief as given in the tables does not bear a relation to the amount of hormone given or to the duration of therapy. So far as is now known, corticotropin and cortisone do not change the underlying disease but control only its manifestations, and it is evident that unless the cause is found and removed asthma will recur.

Although striking improvement is the rule, not all patients are relieved. Severe complications of asthma, particularly emphysema and cor pulmonale, were present in some patients who did not respond. Six of the eight authors cited in Tables 1 and 2 reported deaths, despite treatment with corticotropin or cortisone. Occlusion of the bronchi with extensive mucous plugs is the principal cause of death from asthma. The hormones by themselves are not likely to cause these plugs to loosen. When extensive structural changes are present, and when treatment is started late in an overwhelming attack, these drugs cannot produce miraculous changes; they are not always lifesaving.

One might consider that the stress of long-continued asthma would deplete the adrenal cortex and make it less able to respond to the corticotropin. In practice,

however, this does not seem to be true. The fact that corticotropin works well shows that the adrenal cortex is not destroyed: It can still respond to the stimulation. Our patients do not have Addison's disease.

Comparisons of Corticotropin and Cortisone Effects.—Comparisons of the effects of corticotropin and cortisone do not, however, always give similar results. Not all authors agree on their relative effectiveness. Carey,[13] Feinberg,[14] and Segal [47] have all reported better results with corticotropin than with cortisone. Segal found that corticotropin therapy relieved one patient, after 300 mg. of cortisone given over three and a half days did not; use of corticotropin relieved another when 180 mg. of cortisone given in two days did not, and 150 mg. of cortisone given to a third patient failed to maintain relief established by 510 mg. of corticotropin given over eight days. Cortisone was given intramuscularly, however. A longer course, or larger doses, might have been effective.

On the other hand, Franklin [48] had better results with cortisone. One patient failed to improve when given 80 mg. of corticotropin a day for 11 days, followed by 120 mg. a day for 3 days. Another had no response to 80 mg. of corticotropin a day given for seven days. When 200 mg. of cortisone a day was then given to each, relief followed. Corticotropin was given intramuscularly, as he points out, and no eosinopenia occurred. It is possible that these were examples of failure to absorb the drug. We have seen three patients at the Massachusetts General Hospital who responded only partially to corticotropin, and then were relieved completely by treatment with cortisone. If corticotropin relieves and cortisone does not, the fact suggests that cortisone is not the precisely active principle. The large size of the dose required is another argument for this idea. Obviously, however, cortisone is close to the goal desired.

The level of circulating eosinophiles often falls after the initial doses of hormone, but it is interesting to find that the degree of eosinopenia was of no help in determining the necessary doses. Some of the patients who were not relieved had an eosinophile depression as low as, or lower than, that of those who were completely relieved. Often the eosinophiles rose when the dose of corticotropin or cortisone was reduced, even though the patient remained free of asthma. The correlation between eosinopenia and the clinical response was not regular.

Side-Effects.—Side-effects have made the treatment somewhat hazardous. The selection of patients is important, and the physician must be cautious. As stated in the last review, Thorn has warned that the hormones affect all parts of the body: They affect other endocrine systems, including the thyroid and the gonads; they affect the metabolism of electrolytes, carbohydrates, proteins, and fats; they affect the neuromuscular system, the brain and the muscles; they affect blood cells; they affect enzymes, and they affect antibodies, as described above. Each of these side-effects has been seen in the clinic, but, fortunately, they disappear as soon as the

47. Segal, M. S., and Herschfus, J. A.: ACTH and Cortisone in the Management of the Hypersensitivities, with Particular Reference to Bronchial Asthma: A Review of Clinical and Laboratory Studies, Ann. Allergy **8**:786, 1950.

48. Franklin, W.; Lowell, F. C.; Schiller, I. W., and Beale, H. D.: Clinical Studies with Cortisone by Mouth, Cortisone by Injection, and ACTH in the Treatment of Asthma, J. Allergy **23**:27, 1952.

treatment is discontinued. The important point is to be on guard against them. Hypertension, diabetes, tuberculosis, and peptic ulcer are direct contraindications. A history of serious mental illness in the patient or his family is another.

Nervous effects have been the most serious. Cooke's group [49] and the Friedlaenders [50] each reported on two patients who exhibited a psychosis, and Franklin's group [48] described another. One of Franklin's patients had repeated convulsions. Later, when the sodium intake was rigidly reduced, this patient could tolerate the same doses of cortisone without ill-effects. These complications did not appear to depend upon the duration of treatment, and they were reversible.

Edema occurred fairly frequently, but was never disturbing. It cleared usually when the sodium intake was reduced. Mild acne and hirsutism were noted occasionally.

It is paradoxical that the very drug which relieves allergic manifestations can itself act as an allergen. Two of Segal's [47] patients had nearly fatal anaphylactic shock after repeated courses of corticotropin therapy. Feinberg [51] studied in detail a 60-year-old woman who was given corticotropin for rheumatoid arthritis. Although she had no history of previous injection of pituitary products, the last of 12 daily injections was at once followed by urticaria, angioedema, and shock. About one year later, she took cortisone without difficulty. When still later corticotropin was given once more, urticaria, angioedema, edema of the larynx, asthma, and profound shock developed immediately. Two weeks later, Feinberg found intradermal reactions positive in high dilutions to corticotropin, whether made from pork, beef, or sheep. Sheep peptide, as well as oxytocin injection (pitocin®), chorionic gonadotropic hormone (antuitrin®), vasopressin (pitressin®), and posterior pituitary (pituitrin®), gave smaller reactions. The test reactions to extracts of pork, beef, and sheep muscle were negative. Positive passive transfer reactions were found to pork corticotropin only. These results seem to indicate that the specificity in this case was related to corticotropin, or perhaps to pituitary preparations. Corticotropin provides no more protection against anaphylaxis in human beings than it does in guinea pigs.

One of our patients displayed local lesions at the site of corticotropin injections, similar to those seen in local insulin reactions. McCombs and co-workers [52] have reported similar mild, transient local reactions which occurred commonly. They used a special "Preparation A" estimated to be about twice as active as the Armour standard LA-1-A. When "Preparation C," approximately 15 times as potent, was substituted, no local reactions occurred. This suggests that the impurities in the cruder extract were responsible for these reactions. As repeated courses of corticotropin are administered, one can expect that allergic reactions will become more

49. Cooke, R. A.; Sherman, W. B.; Menzel, A. E. O.; Chapin, H. B.; Howell, C. M.; Scott, R. B.; Myers, P. A., and Downing, L. M.: ACTH and Cortisone in Allergic Diseases: Clinical, Serologic (Electrophoretic) and Immunologic Studies, J. Allergy **22**:211, 1951.

50. Friedlaender, A. S., and Friedlaender, S.: Observations on the Use of ACTH and Cortisone in the Treatment of Asthma, Hay Fever, and Other Allergic Conditions, Ann. Allergy **9**:588, 1951.

51. Feinberg, S. M.; Feinberg, A. R., and Bigg, E.: Allergy to Pituitary Corticotrophic Hormone, J. A. M. A. **147**:40, 1951.

52. McCombs, R. P.; Cleroux, A. P., and Rosenberg, I. N.: Treatment of Bronchial Asthma with Corticotrophin (ACTH), Bull. New England M. Center **12**:187, 1950.

frequent. The intravenous route promises a special hazard. Renold's [45] warning that the patient must be watched carefully for the first 30 minutes of the infusion should be heeded.

The adverse effect of corticotropin and cortisone on infections is now well known. A recent editorial [53] summarized many of the observations. Patients seriously ill with asthma may have active infections in the edematous bronchi or in obstructed sinuses which may be masked by the hormone treatment, to become widespread and threatening.

McCombs, Cleroux, and Rosenberg [52] reported two self-limited febrile illnesses of undetermined origin occurring just after treatment was discontinued. One was in a patient whose asthma did not respond to use of corticotropin, despite clinical and laboratory evidence of an adrenal response. It is interesting to note that, while his temperature remained at 102 F. for several days, his asthma stopped. This might suggest a mechanism other than stimulation of the pituitary-adrenal axis as the explanation for the beneficial effect of fever on asthma.

One of Baldwin and deGara's [54] patients, who also had bronchiectasis, acquired pneumonia with hemolytic streptococci and Friedländer's bacilli in the sputum, but responded quickly to appropriate treatment with antibiotics. Although complications during hormone treatment have been few, some have been serious. This emphasizes again the need for close observation of all patients receiving corticotropin or cortisone.

Maintenance

There are still many patients with persistently distressing and disabling symptoms in whom no cause of their asthma can be discovered, and who are poorly controlled by ordinary symptomatic and nonspecific treatment. Can corticotropin and cortisone given in maintenance doses, much as thyroid is given in myxedema and insulin in diabetes, control asthma indefinitely? So far, there is no evidence that patients with asthma are deficient in any of the adrenal hormones. Maintenance therapy is probably not replacement therapy.

Few studies on maintenance therapy have been reported. Segal [47] attempted prolonged control with repeated short courses of corticotropin. Occasionally he noted a lessened response after the second course, but usually repeated courses were equally affective. Brown [55] likewise used repeated short courses of corticotropin. Neither of these studies has been carried on long enough for final evaluation. Franklin's group [48] reported on 60 patients treated intermittently for 90 to 403 days with corticotropin or cortisone. The results were encouraging. Although relief was not perfect, disability was markedly reduced. The long duration of treatment was not responsible for the side-effects. Baldwin and deGara [54] maintained 9 of their 11 patients by ambulatory treatment with either corticotropin or cortisone for 26 to 206 days after the initial hospital treatment. Five had satisfactory relief, and three of them discontinued use of the drug without relapse. Four were not controlled. Depression occurred in two, and transient hypertension and

53. ACTH and Cortisone in Infection, editorial, New England J. Med. **245**:75, 1951.

54. Baldwin, H. S., and deGara, P. F.: Hospital and Ambulatory Treatment of Asthma and Eczema with ACTH and Cortisone, J. Allergy **23**:15, 1952.

55. Brown, E. A.; Fox, L. A.; Nobili, C.; Norman, P. P.; Norton, R. C., and Ruby, S.: The Use of ACTH in the Treatment of Ambulatory Asthmatic Patients, Ann. Allergy **9**:459, 1951.

edema in one of these. On the whole, the results were not too good. Cooke [49] reported on maintenance treatment of 11 patients with either corticotropin or cortisone, aiming for reasonable comfort rather than for complete relief. This was achieved in all 11 for periods of 2 to 11 months with doses of 25 to 100 mg. daily or every other day. Individual patients demonstrated a wide variability of dose requirements. None of the patients had undesirable side-effects.

McCombs and associates [52] treated four of their patients with daily doses of corticotropin for two and a half to three and a half months. One patient received a single daily dose of 25 mg. Three others received 30, 30, and 45 mg. in divided doses. All did well. When the dose was omitted, or even lowered, the asthma promptly recurred. For his material these doses correspond to 50 to 90 mg. a day of the Armour LA-1-A standard. Moderate acne and transient local urticarial reactions were the only untoward effects. One patient was treated during pregnancy without difficulty.

Irwin and Burrage [56] have controlled six patients with severe intrinsic asthma completely for 10 months, with doses of 37.5 to 100 mg. a day, without important side-effects. Again, daily doses were necessary, and each patient had an individual requirement, which, when lowered, was promptly followed by a return of wheezing. Two patients who received cortisone intramuscularly had local abscesses, and one of these recently acquired acute pyelonephritis. Another patient had a severe febrile illness, which subsided spontaneously. Hemophilus influenzae organisms were recovered from a blood culture. Since it is rare for H. influenzae to cause important invasive infection in the adult, one can speculate upon the role of cortisone.

The value of prolonged treatment with these powerful drugs cannot be judged from these few reports. More must be learned about resistance to the hormones, the damage to the adrenal cortex, the reactions following termination of treatment, and the adverse side-effects.

Maintenance treatment of rheumatoid arthritis has been carried out more extensively, and reports on it are pertinent to this review. Freyberg and co-workers [57] studied 44 patients with rheumatoid arthritis treated 100 to 406 days with 25 to 100 mg. a day of cortisone orally. All but 2 of the 44 were well controlled. The dose requirement paralleled the severity of the arthritis. Complications forced treatment to be stopped in six. Eighteen stopped treatment by choice. After discontinuing treatment, 10 patients had laboratory evidence of depressed adrenal function lasting two to six weeks, but this was not a clinical problem. Five had severe withdrawal or "rebound" symptoms, with difficult emotional readjustment.

Boland and Headley [58] reported on 60 patients with rheumatoid arthritis treated continuously with cortisone for more than six months. Twenty-seven of these were treated for more than a year. Satisfactory control was obtained in 48 of the 60. Those with the milder disease had the best results and the lowest daily requirements.

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56. Irwin, J. W., and Burrage, W. S.: Unpublished data.

57. Freyberg, R. H.; Traeger, G. H.; Patterson, M.; Squires, W.; Adams, C. H., and Stevenson, C.: Problems of Prolonged Cortisone Treatment for Rheumatoid Arthritis: Further Investigations, J. A. M. A. **147**:1538, 1951.

58. Boland, E. W., and Headley, N. E.: Results of Long-Continued Cortisone Administration in Rheumatoid Arthritis, California Med. **74**:416, 1951.

Doses averaged 37.5 to 80.5 mg. a day. Acute stresses, such as infections, overactivity, and emotional upsets, demanded temporarily larger doses. Five patients required gradually increasing doses. Twenty-four of the 60 had undesirable side-effects, and these were generally the patients needing the larger doses. The single serious complication was a vertebral fracture, due in part to osteoporosis. Treatment with the drug was discontinued gradually in 11 patients. All showed decreased adrenal function for 10 to 80 days, as determined by the low level of urinary 17-ketosteroids and corticoids, as well as by a lack of eosinopenia after an injection of corticotropin.

Ward and associates[59] reported on the first 100 patients with rheumatoid arthritis treated at the Mayo Clinic. Seventy-two patients had long-term therapy with cortisone given in three or four daily oral doses for 1 to 12 months. After an initial "suppressive" dose of 37.5 to 200 mg. a day, given over a two-day to two-week period, a "maintenance" dose of 25 to 100 mg. was given. Thirty-eight patients required daily doses of 50 mg. or less; 24 required 62.5 to 75 mg., and 10 required 87.5 to 100 mg. All had satisfactory, although not complete, control. Side-effects did not require treatment to be stopped in any case. These authors concluded that treatment with cortisone in small, varying, individualized doses short of producing significant side-effects can be maintained for a year or longer and seems to be useful in the management of many cases of rheumatoid arthritis.

On the basis of this experience, it seems possible that cortisone maintenance treatment in certain selected cases of severe asthma may likewise be feasible and useful. It is worth considering that a severe "rebound phenomenon" might produce a serious exacerbation and possibly fatal outcome in an asthmatic patient when treatment is discontinued. Keeton and co-workers[60] reported on two patients who had a severe flare-up of dyspnea and collapsed when corticotropin treatment was suddenly withdrawn after it had been given for prolonged periods. It is important to note that Renold and his group[45] have shown that intravenously given corticotropin can restore the depressed adrenal cortical function rather promptly. This technique may be useful in the management of such a crisis. More carefully controlled studies will have to be done before the place of maintenance hormone treatment in asthma can be defined.

From all these sudies, it is evident that corticotropin and cortisone do not cure the underlying disease, but only control its manifestations. While they are valuable therapeutic tools, they do not change the basic approach to the patient who has asthma. The causative factors and complications must still be diligently sought by the taking of a detailed history, careful examination, clinical experiments, and skin tests.

At present, treatment with corticotropin or cortisone is indicated in severe attacks of asthma, but only when the usual regimen fails. It may be useful in chronically ill patients to improve their general health by providing rest and pro-

59. Ward, L. E.; Slocumb, C. H.; Palley, H. F.; Lowman, E. W., and Hench, P. S.: Clinical Effects of Cortisone Administered Orally to Patients with Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **26**:361, 1951.

60. Keeton, R. W.; Best, W. R.; Hick, F. K.; Montgomery, M. M., and Samter, M.: Dramatic Respiratory Symptoms Induced by Sudden Withdrawal of ACTH, J. A. M. A. **146**:615, 1951.

moting nutrition, and sometimes in preparing the chronic asthmatic patient for necessary surgical procedures. Whenever the cause of asthma is simple and fairly easy to identify, as it is in most of the extrinsic allergic cases, the hormones should not be used. It is much simpler to get rid of the cat or dog, for example, than to subject the patient to treatment which may be dangerous. Furthermore, it is very interesting to find that patients with hay fever have been given the treatment with results which are far from perfect—as shown below.

Corticotropin and Cortisone in Hay Fever

Hay fever is perhaps the "purest" of the allergic diseases, and this makes the results of treatment of ragweed hay fever with corticotropin and cortisone of particular interest.

Koelsche and his group at the Mayo Clinic [61] treated six patients with cortisone in doses of 50 to 200 mg. a day for 6 to 21 days. Five had marked to moderate relief. Two patients were given corticotropin in doses up to 100 mg. a day for 2 to 15 days, one with complete, the other with moderate, relief. Schwartz and co-workers [62] treated ragweed hay fever in 25 patients with 100 mg. of cortisone a day. Results were excellent in 15 and good in 6 others. One of the patients with initial failure subsequently responded to a dose of 200 mg. a day. Results appeared after 1 to 72 hours of treatment, but relapse occurred within a day or two after discontinuance of use of the drug. Meantime, these same patients were being treated with pollen extracts as usual.

Friedlaender and Friedlaender [50] gave 100 mg. of cortisone a day to 13 patients and observed good relief in 7, fair relief in 2, and no relief in 4. Sixteen other patients received only 25 mg. a day of corticotropin. The results were good in 1, fair in 1, and poor in 14. In addition, they treated three hospitalized patients with 100 mg. a day of corticotropin, and all had good results. We must note that hay fever usually subsides in a hospital environment. Zeller [63] treated eight patients with an initial dosage of 100 mg. a day of corticotropin, reducing the dosage to 60 mg. a day later on. Seven were relieved temporarily but relapsed when the treatment was stopped or when the dose was reduced. One patient was unaffected by treatment.

Feinberg and his associates [14] treated three patients having moderately severe hay fever with a total dosage of 400 to 620 mg. of corticotropin given over seven to nine days and noted no beneficial results.

Rappaport and colleagues [64] gave corticotropin in doses of 60 mg. a day for four days to 26 patients and noted clinical improvement in only 9. Again, the doses were small and the duration of treatment was short.

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61. Koelsche, G. A.; Maytum, C. K.; Prickman, L. E., and Carryer, H. M.: Use of Cortisone and ACTH in the Management of Nasal Allergy, Ann. Allergy **9**:573, 1951.

62. Schwartz, E.; Levin, L.; Leibowitz, H.; Reicher, J.; Kelly, J. F.; Wallman, M., and Feinblatt, T. M.: Oral Cortisone Therapy in Ragweed Hay Fever, J. Allergy **22**:32, 1952.

63. Zeller, M.: Adrenocorticotropic Hormone (ACTH) Effect on Ragweed Hay Fever, Ann. Allergy **9**:603, 1951.

64. Rappaport, B. Z.; Samter, M.; McGrew, E. A.; Orrico, J. F.; Ehrlich, N. J.; Hartley, H. S.; Lazar, H.; Lubin, J. L., and Scala, R. A.: ACTH in Ragweed Pollinosis: A Histologic, Immunologic and Clinical Study, J. Allergy **22**:304, 1951.

It is evident that corticotropin and cortisone do prevent the symptoms of hay fever temporarily. It is interesting to find, however, that, although hay fever is a milder disease, the dose of hormone required is just as large as in asthma.

Corticotropin and Cortisone in Other Diseases of Allergy

Some of the papers referred to above report experiences with corticotropin and cortisone in other symptom complexes. The striking relief of signs and symptoms and the prompt relapse when the use of hormones is discontinued are essentially similar to the results in asthma and need not be recited in detail. Certain features, however, are of interest.

Vasomotor Rhinitis.—Many of the patients with asthma studied at the Johns Hopkins Hospital had associated vasomotor rhinitis and nasal polyps. Bordley [65] described the disappearance of edema and the return of normal pink color which took place during treatment. Polyps shrank and in some cases disappeared completely, though temporarily. He treated one patient with a nasal spray containing 8 mg. per cubic centimeter of cortisone and saw a marked regression in size of the polyps within three weeks. The posterior polyps showed slower changes than the anterior ones, which suggested a direct local effect. Baldwin and deGara [54] have not observed polyps to disappear. The simultaneous improvement in the vasomotor rhinitis and asthma is another indication that the nasal changes are a part of the disease, rather than a cause of the asthma.

Eczema.—Glaser [66] found that children with atopic eczema responded well to corticotropin and cortisone but required larger doses in proportion to body weight than did adults. Lever [67] believed the "rebound" following treatment was more likely to be severe in eczema.

Downing, in his excellent review,[68] concluded that corticotropin and cortisone are of dubious value in atopic dermatitis because of the high doses necessary and the consequent potential dangers, especially the frequent emotional depression which may develop with relapse after treatment is stopped. The hormones should be used only in the severest cases when all conventional treatment has failed to arrest the progress of the disease, and even then they should not be given for longer than four to six weeks.

Carey and associates [17] recorded some interesting clinical experiments. One patient who had severe urticaria after penicillin administration was given corticotropin, and the urticaria cleared. During that treatment, he could take 100 units and later 1,000 units of aqueous penicillin without reaction. Another patient, also sensitive to penicillin, was treated similarly. When his hives cleared, he was given penicillin again—5,000 units and then 50,000 units. This time, slight local redness and itching developed, but there was no general urticaria.

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65. Bordley, J. E.: Observations on Changes Taking Place in the Upper Respiratory Tract of Patients Under ACTH and Cortisone Therapy, Bull. Johns Hopkins Hosp. **87**:415, 1950.

66. Glaser, J.; Siegal, S. C.; Goldstein, J. D., and Meltzer, R. S.: Experiences with ACTH and Cortisone in the Treatment of Asthma and Eczema in Infancy and Childhood, Ann. Allergy **9**:292, 1951.

67. Lever, W. F.: ACTH and Cortisone in Diseases of the Skin, New England J. Med. **245**:359, 1951.

68. Downing, J. G.: The Use of ACTH and Cortisone in Dermatology, New England J. Med. **246**:56, 1952.

A patient with atropine dermatitis of the eyelids was completely relieved by administration of corticotropin. The previously positive patch-test reaction became negative. While continuing corticotropin therapy, use of atropine eye drops was resumed, and no new dermatitis developed.

A patient with chronic asthma was known to be sensitive to acetylsalicylic acid. While receiving 140 mg. of corticotropin daily, which relieved the asthma, he was given 130 mg. of acetylsalicylic acid by mouth. An attack of asthma came 130 minutes later, severe enough to require intravenous injection of aminophylline. The following day, administration of 64 mg. of acetylsalicylic acid was followed by a mild attack of asthma after 150 minutes. He was then given 32 mg. of acetylsalicylic acid daily while the dose of corticotropin was gradually reduced, and after that he had no further reactions. Ten days after the last dose of corticotropin, he was challenged with 80 mg. of acetylsalicylic acid, and no asthma developed.

Salen [69] did not find that corticotropin protected against asthma induced by acetylsalicylic acid.

These studies suggest the interesting possibility of desensitization during hormone treatment, particularly in conditions in which it is important to use the offending drug, atropine in iritis, for example.

Eye Diseases.—Nongranulomatous iritis is believed to be sometimes due to bacterial hypersensitivity. The inflammatory phase of ocular tuberculosis seems to depend upon tuberculin sensitivity. There is evidence that sympathetic ophthalmia, a self-limited disease, but often ending in blindness, may be a sensitivity to the patient's own uveal pigment. Harvey and associates [70] reported the remarkable effect of corticotropin therapy and cortisone in these diseases. The effect was particularly impressive in three cases of sympathetic ophthalmia in which vision was apparently saved. When cortisone can be applied directly to the area of inflammation, it is said to be just as effective locally as when it is given systemically. Smith and Steffensen [71] have recently reviewed the literature on the use of corticotropin and cortisone in eye diseases. They also listed reports of successful hormone treatment in these conditions, as well as in vernal conjunctivitis, phlyctenular conjunctivitis, and marginal corneal ulcers, each of which have elements of allergic reactions in their mechanism. While most of these conditions are self-limited, the acute stages of drug reactions, contact dermatitis, and some eye diseases may be so damaging that the control of the acute allergic inflammation becomes of great practical importance.

Periarteritis Nodosa.—Mundy and his associates [72] reviewed the reports on treatment of periarteritis nodosa with corticotropin and cortisone and added a case: A 50-year-old man having severe asthma and periarteritis nodosa was treated with four

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69. Salen, E. B.: Oral Administration of Cortisone (Cortone) in Bronchial Asthma, Acta allergol. **4**:223, 1951.

70. Harvey, A. M.; Howard, J. E., and Kattus, A. A.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Certain Diseases of the Eye in Which Hypersensitivity Plays a Role, Bull. Johns Hopkins Hosp. **87**:461, 1950.

71. Smith, R. W., Jr., and Steffensen, E. H.: ACTH and Cortisone in the Treatment of Ocular Disease, New England J. Med. **245**:972, 1951.

72. Mundy, W. L.; Walker, W. G.; Bickerman, H. A., and Beck, G. J.: Periarteritis Nodosa: Report of a Case Treated with ACTH and Cortisone, Am. J. Med. **11**:630, 1951.

separate courses of corticotropin or cortisone over 17 months. Temporary remission of both the asthma and the manifestations of periarteritis nodosa occurred with each course.

Rosenberg and co-workers [73] also reported on three patients treated with corticotropin. Two patients with far-advanced disease had little benefit, but one patient treated after only two months of symptoms enjoyed a remarkable clearing of both symptoms and signs.

The results have been promising when periarteritis nodosa was treated early. In most cases complete resolution of lesions cannot be expected. Hormone-treated patients examined at autopsy have shown lesions which have healed, but with fibrosis, obliteration of blood vessels, and consequent infarctions of the tissues supplied.

The changes of periarteritis nodosa are so similar to the vascular lesions of experimental serum sickness that allergy seems to be at least a possible factor in some cases. In his excellent review of drug allergy, Carr [74] has listed drugs which have been implicated in individual cases. Best and Fine [75] reported periarteritis nodosa occurring in a 53-year-old man who also had multiple myeloma which was treated with stilbamidine. The first dose was followed by febrile episode. After improvement, another intravenous injection of stilbamidine was given a month later. Fever recurred, and the man died. While additional treatment with penicillin, streptomycin, and blood transfusions complicated the picture, the reactions after each of two different doses of stilbamidine raise the question of allergy to this drug.

The premise that drug allergy may cause periarteritis nodosa suggests the particular value of corticotropin or cortisone in such cases. If treatment can be started early, a cure may result, for drug allergy should be a self-limited process. It becomes important to look for drug allergy in every case of suspected periarteritis nodosa.

Experimental Hypersensitivity

A review of certain studies in the laboratory sheds some light on the mechanism of human allergic diseases, for some of the pathologic changes are similar.

Stetson and Good [76] have carried out a series of experiments which demonstrate the similarities of the Shwartzman phenomenon and the Arthus reaction and emphasize the role of the polymorphonuclear leucocytes. First, they showed that glycogen in the prepared skin site underwent glycolysis, and that this chemical reaction is concerned with injury to blood vessels in the area, which increases the tendency to thrombosis. Next they found that leucocytes were necessary, for when the level was extremely reduced in both blood and tissues by the toxic action of nitrogen mustard (methyl *bis* or *tris* [β-chloroethyl]amine hydrochloride), the Shwartzman phenomenon could not be elicited. In an ingenious experiment, they clamped the aorta during the injection of nitrogen mustard, so that the drug could not reach the femoral bone marrow. Leucopenia did not develop, and the Shwartzman phenomenon appeared as usual.

73. Rosenberg, I. N.; Cleroux, A. P.; Raben, M. S.; Payne, R. W., and Astwood, E. B.: Clinical Evaluation of Corticotropin Therapy, A. M. A. Arch. Int. Med. **88**:211, 1951.

74. Carr, E. A.: Allergy to Drugs, New England J. Med. **245**:892, 1951.

75. Best, W. R., and Fine, G.: Periarteritis Nodosa and Multiple Myeloma: Report of Simultaneous Occurrence in a Patient Receiving Stilbamidine, Ann. Int. Med. **34**:1472, 1951.

76. Stetson, C. A., Jr., and Good, R. A.: Studies on the Mechanism of the Shwartzman Phenomenon: Evidence for the Participation of Polymorphonuclear Leucocytes in the Phenomenon, J. Exper. Med. **93**:49, 1951.

When toxic substances capable of eliciting the Shwartzman phenomenon are injected intravenously into normal rabbits, leucocytes and thrombocytes diminish in the peripheral blood; they pool in the lung capillaries and perhaps elsewhere.

These events occur in the Arthus reaction as in the Shwartzman phenomenon.[77] In each case, there are hematologic, metabolic, and histologic patterns which are entirely similar.

Stetson [78] considered that both the Arthus and the Shwartzman phenomena are the result of two separate processes. The first is a local change which makes the blood vessels more susceptible to thromboses. The second is a systemic change, causing generalized intravascular clumping of leucocytes and thrombocytes. Some of these clumps collect in the damaged vessels to form thrombi, with later hemorrhage and necrosis. In the Shwartzman phenomenon, the injury is a direct toxic effect; it is nonspecific. In the Arthus reaction the injury is secondary to an antigen-antibody reaction, which is specific. The local and systemic reactions take place simultaneously in the Arthus reaction.

That the leucocytes play an essential role is evident. In the Arthus reaction, nitrogen mustard not only depresses leucocytes, but inhibits antibodies also, as Dammin and Bukantz [79] and Schwab and associates [80] have shown. The process is not a simple one.

As noted above, Ebert and Wissler [42] observed in the living animal similar intravascular clumping of thrombocytes and leucocytes after large intravenous doses of horse serum. They also saw focal endothelial swelling with sticking of leucocytes. Much the same type of lesion was reported by DeMuro and Focosi,[81] who observed thrombocyte thrombi of the retinal veins after a challenging dose injected directly into the vitreous in rabbits sensitized to horse serum.

Thomas' experiments [82] are interesting. Injections of hemolytic streptococci into the skin of normal rabbits cause infections which remain localized. When the animals are treated with cortisone, the local skin infection becomes generalized and lethal. Focal masses of streptococci are found in the heart muscle. Making use of the fact that intradermal streptococcal infections are good preparatory sites for the Shwartzman phenomenon, he treated normal rabbits with cortisone. Skin sites were then prepared by injecting beta hemolytic streptococci intradermally, and finally a Gram-negative bacterial toxin was given intravenously. In these ani-

77. Stetson, C. A., Jr.: Studies on the Mechanism of the Shwartzman Phenomenon: Certain Factors Involved in the Production of the Local Hemorrhagic Necrosis, J. Exper. Med. **93**:489, 1951.

78. Stetson, C. A., Jr.: Similarities in the Mechanisms Determining the Arthus and Shwartzman Phenomena, J. Exper. Med. **94**:347, 1951.

79. Dammin, G. J., and Bukantz, S. C.: Modification of Biologic Response in Experimental Hypersensitivity, J. A. M. A. **139**:358, 1949.

80. Schwab, L.; Moll, F. C.; Hall, T.; Brean, H.; Kirk, M.; Hawn, C. V., and Janeway, C. A.: Experimental Hypersensitivity in the Rabbit: Effect of Inhibition of Antibody Formation by X-Radiation and Nitrogen Mustards on the Histologic and Serologic Sequences, and on the Behavior of Serum Complement Following Single Large Injections of Foreign Proteins, J. Exper. Med. **91**:505, 1950.

81. DeMuro, P., and Focosi, M.: Vascular Allergy: Experimental Studies on Allergic Thrombosis of the Retinal Veins, J. Allergy **22**:114, 1951.

82. Thomas, L.: The Production of Cardiac Lesions Resembling Acute Rheumatic Carditis by Streptococcal Infection and a Modification of the Shwartzman Reaction, J. Lab. & Clin. Med. **38**:955, 1951.

mals, hemorrhagic necrotic lesions developed in the skin and also in the myocardium—evidently a Shwartzman phenomenon in the heart. Hemorrhages throughout the heart muscle, necrosis of myofibrils, and perivascular deposition of fibrinoid substance were seen. In addition, there was an accumulation of "owl-eyed" cells and multinucleated giant cells, strikingly similar to the lesions of rheumatoid carditis in human beings.

These changes of experimental hypersensitivity are comparable with those of some human diseases. Stetson [83] studied the hearts of several patients who had died with rheumatic carditis. He found masses of thrombocytes and leucocytes more or less completely filling the lumina of the small vessels in all the six patients who died with early acute carditis. He observed the masses in two of six patients with chronic rheumatic carditis and in two of three with subacute bacterial endocarditis. The thrombi were located chiefly in the small veins and capillaries and only occasionally in the arterioles. They were similar in appearance to the experimental lesions. Aschoff bodies were observed in all the hearts which showed thrombi, but in none of the others. The hearts of 16 patients with miscellaneous diseases, including 1 with periarteritis nodosa and 1 with chronic glomerular nephritis, showed no thrombocyte-leucocyte thrombi.

McKinlay [84] reported the case of a man who had cardiac enlargement, signs of pericarditis, and a left pleural effusion during the course of serum sickness following an injection of tetanus antitoxin. He recovered. About a month later follicular tonsillitis developed, with fever, headache, and vomiting. In six days, pericarditis and myocarditis recurred, with fever, cardiac enlargement, gallop rhythm, and electrocardiographic changes. He subsequently made a complete recovery. It is tempting to postulate a mechanism similar to that in Thomas' rabbits, a variety of the Shwartzman phenomenon.

Luce, Leith, and Burrage [85] reported two cases of sterile meningitis following use of ethyl iodophenylundecylate (pantopaque®) for myelograms. Intradermal tests with ethyl iodophenylundecylate made just before the intrathecal injection gave negative reactions. Meningitis occurred 9 days later in one and 30 days later in the other. After recovery, intradermal tests with ethyl iodophenylundecylate gave delayed inflammatory reactions in both. The authors considered the possibility of a Shwartzman phenomenon in this case, but the course seemed more consistent with a serum-sickness-like reaction produced by the ethyl iodophenylundecylate antigen remaining in the cerebrospinal fluid.

Thrombotic thrombopenic purpura is a rare disease characterized by thrombocytopenia, hemolytic anemia, and central nervous system changes.[86] The widespread accumulation of thrombocytes in thrombocyte thrombi of small vessels seems to explain the thrombocytopenia. A hypersensitive mechanism has been postulated as a possible factor. Gore [87] has studied the pathologic changes in five cases

83. Stetson, C. A.: The Occurrence of Leucocyte-Platelet Thrombosis in Rheumatic Carditis, J. Exper. Med. **94**:493, 1951.

84. McKinlay, C. A.: Transient Periods of Cardiac Enlargement Associated with Hypersensitivity to Different Etiologic Agents: Report of a Case, Ann. Int. Med. **35**:226, 1951.

85. Luce, J. C.; Leith, W., and Burrage, W. S.: Pantopaque Meningitis Due to Hypersensitivity, Radiology **57**:878, 1951.

86. Thrombotic Thrombocytopenic Purpura, editorial, Ann. Int. Med. **33**:739, 1950.

87. Gore, I.: Disseminated Arteriolar and Capillary Platelet Thrombosis: A Morphologic Study of Its Histogenesis, Am. J. Path. **26**:155, 1950.

thoroughly and described a focal subendothelial swelling of capillaries and arterioles in which thrombocytes accumulated but inflammatory changes were conspicuous by their absence.

Wallace [88] reported two cases of the syndrome. In each there were similar foci of thrombocyte thrombi without inflammation of the vessels, but, in addition, other areas showed perivascular changes typical of periarteritis nodosa. Symptoms in one of the cases began after penicillin treatment of a skin infection, and then became much worse when later on penicillin was given again. In the second case both penicillin and a sulfonamide had been given for a throat infection, and purpura developed. Evidently periarteritis nodosa and thrombotic thrombocytopenic purpura have features in common.

Idiopathic thrombocytopenic purpura is a different disease, but it also may have an allergic component. Hirsch and Dameshek [89] divided their 89 cases into two groups. In one group the disease is an acute self-limited one which clears within a few months and is associated often with drug allergy or with an acute infection. In the other group the disease is a chronic process which comes and goes for years. Eosinophilia is found in the acute disease, but not in the chronic form. Splenectomy, which is often curative in the chronic type, is not indicated in the acute type.

Nitrogen Mustard.—Nitrogen mustard has been given to patients for asthma. In addition to its toxic effect on the bone marrow, Jimenez-Diaz [90] found that nitrogen mustard produced adrenal hyperplasia, increased 17-ketosteroid excretion, and prevented experimental asthma in guinea pigs. It stimulated the pituitary-adrenal mechanism. He treated 13 patients who had chronic persistent asthma with three to four injections of nitrogen mustard in doses of 4 to 6 mg. each, on alternate days. Ten of the 13 were completely relieved, 1 was greatly improved, and 2 were unchanged. Leucocytes and eosinophiles fell, and the urinary 17-ketosteroid excretion was increased. The relation of these changes, particularly of the leucopenia, to the duration of remission would have been of interest. Incidentally, 32 patients with rheumatoid arthritis also had good, but less consistent, relief after similar treatment.

The Allergic State

Rackemann's review of 1951 [1] called attention to the clinical concept of the "allergic constitution." Certain persons have a special background upon which hay fever, asthma, or eczema can develop. Two recent papers present laboratory evidence which furthers this theory.

Kuhns, Lawrence, and Pappenheimer [91] observed that when normal and allergic persons were hyperimmunized with diphtheria toxoid there was a considerable discrepancy in the location of the antitoxin. In the normal persons, the antitoxin

88. Wallace, D. C.: Diffuse Disseminated Platelet Thrombosis (Thrombotic Thrombocytopenic Purpura) with a Report of 2 Cases, M. J. Australia **2**:9, 1951.

89. Hirsch, E. O., and Dameshek, W.: "Idiopathic" Thrombocytopenia: Review of 89 Cases with Particular Reference to the Differentiation and Treatment of Acute (Self-Limited) and Chronic Types, A. M. A. Arch. Int. Med. **88**:701, 1951.

90. Jimenez-Diaz, C.: Treatment of Dysreaction Diseases with Nitrogen Mustards, Ann. Rheumat. Dis. **10**:144, 1951.

91. Kuhns, W. J.; Lawrence, H. S., and Pappenheimer, A. M., Jr.: Immunochemical Properties of Antitoxin in Normal and Allergic Individuals Hyperimmunized with Diphtheria Toxoid, Federation Proc. **10**:413, 1951.

was found in the precipitable gamma globulin. In the allergic persons, however, most of the antitoxin remained in the supernatant fluid after the globulins had been precipitated away. One such patient with 50 units per milliliter in his blood had no precipitable antitoxin, and yet his serum contained skin-sensitizing antibodies to toxin in high titer. The antitoxin was concerned with the nonprecipitable fraction. Cregar, Choy, and Rantz [92] studied the production of both influenza A and B antibodies and isohemagglutinins to heterologous human blood groups in 48 healthy students. Two of these students formed excessive amounts of both influenzal and hemagglutinating antibodies, and then it was found that both of them had had severe reactions to previous serum therapy: They were "allergic."

A small group of patients with diseases related to hypersensitivity, such as disseminated lupus, erythema nodosum, and active rheumatic fever, also produced high isohemagglutinin titers. In addition, these hyperreactors formed large amounts of "hyperimmune type" (Marack's No. 3) antibody.

Thus, the antibodies in the blood, as well as the reaction in the tissues, may be altered in the allergic state.

Asthma

Physiology of Respiration.—Several interesting seminars on the physiology of respiration have been published in *The American Journal of Medicine* during the past year. Segal, Herschfus, and Bresnick [93] have reviewed the literature of pulmonary function studies in asthma and have added observations of their own.

The pathophysiology of the attack of asthma is similar to that of emphysema. The total lung capacity is increased; the lungs are distended. The functional residual capacity, the amount of air remaining in the lungs and bronchi after ordinary expiration, is increased. Intrapulmonary mixing, as determined by the amount of nitrogen remaining in the alveolar air after breathing 100% oxygen for seven minutes, is less efficient; the nitrogen figure is high; the "index" is increased. The expiratory velocity is slowed. The point is that air is trapped in the lungs. The maximum breathing capacity, which depends partly on voluntary effort, is reduced to a greater degree than is the vital capacity. The arterial oxygen saturation may be reduced without a significant change in the arterial pH or carbon dioxide tension, since carbon dioxide diffuses more readily than does oxygen. In asthma, mucosal edema, thick mucoid secretions, and bronchospasm cause obstruction to the airflow. In emphysema, there are destruction of alveoli and diminished elasticity, with consequent overdistention of the lungs and great trapping of air.

Lukas [94] and Beale, Fowler, and Comroe [95] have studied pulmonary function during asymptomatic phases of patients with asthma. Most of them were young persons who had moderate or severe asthma with frequent attacks. Both groups of investigators found diminished function to be the rule. Use of ephedrine, epi-

92. Cregar, W. P.; Choy, S. H., and Rantz, L. A.: Experimental Determination of the Hypersensitive Diathesis in Man, J. Immunol. **66**:445, 1951.

93. Segal, M. S.; Herschfus, J. A., and Bresnick, E.: Pulmonary Function Tests in Bronchial Asthma, Ann. Allergy **9**:796, 1951.

94. Lukas, D. S.: Pulmonary Function in a Group of Young Patients with Bronchial Asthma, J. Allergy **22**:411, 1951.

95. Beale, H. D.; Fowler, W. S., and Comroe, J. H., Jr.: Pulmonary Function Studies in 20 Asthmatic Patients in the Symptom-Free Interval, J. Allergy **23**:1, 1952.

nephrine, or aminophylline caused improvement, but usually even these measures did not produce a complete return to normal. Lukas, however, did observe a more striking improvement after treatment with corticotropin or cortisone.

Lukas [94] performed cardiac catheterization in one of his patients, a girl of 15 who had had frequent attacks of asthma since the age of 8 years. She had polycythemia, cyanosis, electrocardiographic evidence of right ventricular hypertrophy, a vital capacity of 38%, arterial oxygen saturation of 84%, and normal arterial pH and carbon dioxide content. He recorded a normal cardiac output at rest with an appropriate increase on mild exercise. The mean pulmonary arterial pressure at rest was somewhat elevated, 22 mm. Hg as compared with the upper normal of 15 mm. Hg. During exercise, it increased to a mean of 28 mm. Hg, and this is significant, since normally the pulmonary arterial pressure does not increase until the cardiac output rises threefold above the resting value. The pulmonary vascular resistance was estimated to be increased to twice its normal value. Since this girl had only a slight improvement after epinephrine treatment, and since her total lung capacity was smaller than the predicted normal, it is probable that irreversible emphysema and fibrosis were present to cause the increase in pulmonary artery pressure.

When compared with the values found in mitral stenosis, however, the pulmonary artery pressure in this girl is not particularly high. In mitral stenosis, Gorlin and his co-workers [96] reported an average mean pulmonary artery pressure of 42 mm. Hg at rest and 62 mm. Hg after exercise.

The variations in the pulmonary artery pressures, as well as other changes in the pulmonary circulation during attacks of uncomplicated asthma, are not yet understood. Hamilton's review [97] is helpful.

Thus, the changes of asthma are not quite so reversible as previously believed, at least when attacks are severe and prolonged. Beale's group [95] and Lukas [94] both believed that pulmonary function tests have a practical application in the treatment of asthma. If between attacks function is not normal, there must be a reason. The discovery and then the elimination of local areas of obstruction which may lead to infection, fibrosis, and emphysema may prevent the irreversible changes that cause so much disability. Furthermore, since local obstructions could prevent aerosol medication from reaching the areas where it is most needed, systemic medication seems more reasonable.

Wilson, Borden, and Ebert [98] studied the adaptation to anoxia in patients with chronic pulmonary emphysema. They found that, in general, neither the hemoglobin concentration nor the marrow activity is increased. All their patients had normal, or even low, hemoglobin levels. This contrasts with the response of residents of high altitudes, in whom compensatory polycythemia quickly develops in response to lowered oxygen tension. The reason for this lack of response in emphysema is obscure, especially as patients with pulmonary fibrosis and congenital heart disease do have polycythemia, often to advanced degrees.

96. Gorlin, R.; Sawyer, C. G.; Haynes, F. W.; Goodale, W. T., and Dexter, L.: Effects of Exercise on Circulatory Dynamics in Mitral Stenosis, Am. Heart J. **41**:192, 1951.

97. Hamilton, W. F.: The Physiology of the Pulmonary Circulation, J. Allergy **22**:397, 1951.

98. Wilson, R. H.; Borden, C. W., and Ebert, R. V.: Adaptation to Anoxia in Chronic Pulmonary Emphysema, A. M. A. Arch. Int. Med. **88**:581, 1951.

Treatment.—Oxygen, which has such widespread use, may be dangerous when given to patients with pulmonary disease that is severe enough to cause a retention of carbon dioxide and respiratory acidosis. Schiller and associates [99] described two such patients with asthma who lapsed into coma when oxygen was given, and who recovered consciousness when use of oxygen was discontinued. Their studies in both patients showed that the added oxygen raised the low arterial oxygen saturation so that the cyanosis cleared. At the same time, however, the removal of the stimulus to breathing made the arterial carbon dioxide pressure rise and the blood pH fall. These changes could be reproduced at will. We, too, have seen coma develop when oxygen was administered to three patients whose asthma was desperately severe, and we found that the coma and the cyanosis came and went as the oxygen was turned on or off. When later a nasal catheter was arranged, the amount of oxygen given through it could be adjusted at a midpoint between coma on the one hand and cyanosis on the other.

Pulmonary function studies in one of Schiller's patients showed that when oxygen was added the respiratory minute volume was unchanged, although the respiratory rate rose from 22 to 28 per minute. The volume of each breath, the tidal volume, decreased considerably, from 370 to 290 cc. Since the dead space is believed to be about 200 cc., it is startling to find that the amount of air passing into the lungs is so small.

The respiratory center in the medulla is stimulated both directly by increasing arterial carbon dioxide tension and reflexly by anoxia through receptors in the carotid and aortic bodies. When arterial carbon dioxide levels are high, the respiratory center is first stimulated maximally and later depressed. Thus, the theory goes that when the remaining stimulus of anoxia is removed by treatment with oxygen the additional stimulus from the carotid and aortic bodies is removed. Respiration becomes more shallow; carbon dioxide accumulates further, and carbon dioxide narcosis develops.

It is also quite possible that the dangers of the use of morphine and meperidine (demerol®) hydrochloride in asthma depend upon this same mechanism, for these drugs are well-known respiratory depressants.

Walton, Penner, and Wilt [100] reported the clinical and pathologic observations on 13 patients who died suddenly in an attack of asthma. All showed voluminous lungs and diffuse bronchial plugging with tenacious mucus. Opiates, including meperidine, had been given to six of these patients shortly before death, and large doses of barbiturates had been given to two others. Walton discussed the likely possibility that meperidine and morphine were responsible for the fatal outcome and stressed the danger of heavy sedation in severe asthma.

Two patients died suddenly after the local application of tetracaine (pontocaine®) hydrochloride in preparation for bronchoscopy. Walton pointed out that ether should be the anesthetic of choice in such procedures.

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99. Schiller, I. W.; Beale, H. D.; Franklin, W.; Lowell, F. C., and Halperin, M. H.: The Potential Danger of Oxygen Therapy in Severe Bronchial Asthma, J. Allergy **22**:423, 1951.

100. Walton, C. H. A.; Penner, D. W., and Wilt, J. C.: Sudden Death from Asthma, Canadian M. A. J. **64**:95, 1951.

Our experience at the Massachusetts General Hospital has been similar. We have seen disaster follow the use of meperidine in patients who came to the emergency ward with severe asthma. We have also seen sudden death following topical anesthesia prior to bronchoscopy. We agree heartily with Walton's warnings.

Acetylsalicylic Acid.—Acetylsalicylic acid, another simple and useful drug, may be harmful to patients with asthma. Walton and Bottomley [101] reviewed observations on 830 successive patients with asthma and found that 22 (2.7%) were sensitive to acetylsalicylic acid. One of these had a near-fatal reaction after taking a single pill. This experience in general tends to support the belief that acetylsalicylic acid sensitivity has a serious prognostic significance, for the asthma in 11 of these 22 patients was severe. So far, no way has been found to determine acetylsalicylic acid sensitivity in patients. Matthews, Lovell, and Sheldon [102] studied a group of 12 acetylsalicylic-acid-sensitive patients, using a variety of methods. Both scratch and intradermal tests with sera obtained from patients who were receiving large doses of acetylsalicylic acid failed to produce positive reactions. Sera from the acetylsalicylic-acid-sensitive patients injected intradermally into other acetylsalicylic-acid-treated patients likewise failed to show reactions. Passive transfer tests were also futile. It seems that the clinical history and the hazardous provocative test remain the only methods of diagnosing acetylsalicylic acid sensitivity.

Feinberg and Malkiel [103] sensitized both guinea pigs and rabbits by the injection of acetylsalicylic acid-protein conjugates. The sera of sensitized rabbits showed precipitating antibodies to acetylsalicylic acid, as well as to sodium salicylate. In another experiment, guinea pigs, passively sensitized with serum from acetylsalicylic-acid-sensitive patients, could be shocked when challenged with heterologous acetylsalicylic acid-protein conjugate.

Khellin.—Khellin, a drug manufactured from the seeds of a Mediterranean plant, can relax smooth muscle. Anrep and colleagues [104] have previously reported its effectiveness in asthma. Derbes and co-workers [105] treated 45 asthmatic patients with khellin in doses of 100 mg. a day and noted excellent relief in 10, good relief in 16, and no effect in 19. The oral and intramuscular routes seemed equally effective. Nausea is the chief side-reaction. No pressor effect on blood pressure was observed.

Rosenman and others [106] also treated asthma with khellin, using a single intramuscular injection of 200 mg. Nine of 21 patients improved, often dramatically. In addition, they gave khellin by mouth to eight patients who had chronic pulmonary

101. Walton, C. H. A., and Bottomley, H. W.: Allergy to Aspirin, Canadian M. A. J. **64**:187, 1951.

102. Matthews, K. P.; Lovell, R. G., and Sheldon, J. M.: The Problem of Aspirin Allergy with a Report on Skin Testing with Salicylate-Containing Human Sera, J. Lab. & Clin. Med. **36**:416, 1950.

103. Feinberg, A. R., and Malkeil, S.: Aspirin Sensitivity—Experimental Studies, J. Allergy **22**:74, 1951.

104. Anrep, G. V.; Barsoum, G. S.; Kenawy, M. R., and Misrahy, G.: Therapeutic Uses of Khellin: Method of Standardization, Lancet **1**:557, 1947.

105. Derbes, V. J.; White, R. J.; Teverbaugh, J.; Vaughan, D. D., and Weaver, N. K.: Observations on the Action of Khellin in Attacks of Bronchial Asthma, Ann. Allergy **9**:354, 1951.

106. Rosenman, R. H.; Fishman, A. P.; Kaplan, S. R.; Levin, H. G., and Katz, L. N.: Observations on the Clinical Use of Visammin (Khellin), J. A. M. A. **143**:160, 1951.

disease with cor pulmonale. All showed distinct improvement in breathing, color, and exercise capacity when receiving 100 to 300 mg. a day. Those patients who had right ventricular failure showed diminished edema.

Because of the unexpected effect, Silber and associates [107] studied six patients with chronic pulmonary disease by cardiac catheterization before and after single doses of khellin given intramuscularly. They observed no consistent changes at rest or during exercise. When khellin was then given orally for four to seven days, all six patients felt better, but the only measurable change was an increase in the maximum breathing capacity in four patients. No consistent changes were found in ventilation, oxygen uptake, oxygen removal, cardiac output, or pulmonary artery pressures. The studies indicate that the bronchorelaxing action of khellin is its only effect. Whether khellin will become useful in the clinic remains to be seen.

Derbes, Weaver, and Cotton [108] have written a timely review of the complications of asthma. They discussed bronchostenosis and infection, bronchiectasis, Loeffler's syndrome (eosinophilic pneumonitis), tuberculosis, pulmonary interstitial and mediastinal emphysema, spontaneous pneumothorax, and cor pulmonale, as well as other lesions. This paper emphasized that when the patient with asthma is not doing well the presence of some complicating disease may explain the lack of response to treatment. Sometimes the basic disease—tuberculosis, for example—may explain the whole picture.

CONCLUSIONS

Since their discovery in 1949, corticotropin (ACTH) and cortisone have been found to be effective in asthma, as in many other diseases. Although many studies of the action of these hormones have been carried out, the precise mechanism of their beneficial effects is not yet known. On anaphylactic shock, in animals or in man, there is no effect; on passive anaphylaxis, there is no effect, but on the Arthus reaction there is an effect, as Germuth and associates could show. If different types of antibody are responsible for these different reactions, it may be that the hormones act on one type more than on another. On skin tests in man, as well as on the "reagins" which transfer skin sensitivity, there is no effect. On histamine reactions, there is no effect. So far, the Arthus reaction stands out as an exception, unless it be that the variations depend on differences of quantity rather than of quality. Note, for example, the experiments of Bjørneboe and colleagues which showed that antibodies to Pneumococcus immunization were reduced. Additional studies of the nonprecipitating univalent antibody will be helpful. So far the impression is that on the basic immunologic mechanism of asthma, of hay fever, of urticaria, and of eczema, the steroid hormones have no direct effect, but new techniques may change this impression.

Meantime, and in contrast, the inflammation of the tuberculin reaction and of other bacterial processes similar to it are modified. The Shwartzman phenomenon with its local inflammation is reduced in severity. The nonspecific effect of the hormones on the local reaction is real.

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107. Silber, E. N.; Snider, G. L.; Goldberg, H.; Katz, L. N., and Radner, D. B.: The Effect of Khellin on Cardiopulmonary Function in Chronic Pulmonary Disease, J. Clin. Invest. **30**:1046, 1951.

108. Derbes, V. J.; Weaver, N. K., and Cotton, A. L.: Complications of Bronchial Asthma, Am. J. Med. Sc. **222**:88, 1951.

The characteristic chain of events which Rich and his associates demonstrated in anaphylaxis—the changes in the walls of blood vessels, with hemorrhage and local lesions later—seemed to explain the pathology of periarteritis nodosa, and these changes could be inhibited by cortisone treatment. With their rabbit ear chamber, Ebert and Wissler could actually see the "sticking" of leucocytes, the "sludging" of red cells, and the formation of the leucocytes-thrombocyte thrombi, and they, too, could inhibit the process by treatment of the rabbits with cortisone. Stetson's studies of the Shwartzman phenomenon reveal a series of processes which is similar. It is interesting indeed to find that a pattern of reaction underlies all these phenomena, and that it is uniform. While both corticotropin and cortisone inhibit all these reactions, one must note that the inhibitions are temporary in each case; as soon as use of the drug is discontinued, the reaction proceeds at its normal pace. Some day a series of clever experiments will show just how corticotropin and cortisone exert their effect.

In the clinic, the experience is quite analogous. In the simple type of allergic asthma as it occurs in young persons, as well as in hay fever, the hormones are not effective until large doses have been administered. In these "pure" allergic conditions, the drugs are not very useful. In the older group, however, in which the asthma is intrinsic and associated with exhaustion or "depletion" of the patient, and perhaps also with tissue changes, the drugs are useful. Whenever asthma is very severe, the use of corticotropin or cortisone should be considered, but one must note that treatment with the hormones is not always lifesaving. So far, the good effect seems to depend upon a "nonspecific factor" of unknown character. It is tempting to consider that the hormones can correct a disturbance in the adrenal cortex and an alteration in its normal functions, but it will take many more observations to show that such a consideration is justified.

Other advances are being made. New drugs are being investigated, and the clinical studies of asthma and its complications are being pursued. This is good, because at this time of writing corticotropin and cortisone are not the final answer.

News and Comment

ANNOUNCEMENTS

Clinical Congress of American College of Surgeons.—The 38th annual Clinical Congress of the American College of Surgeons will be held in New York City Sept. 22 to 26, 1952. The program will include panel discussions, symposia, surgical forums, motion pictures, cine clinics, color television, and exhibits. Headquarters will be at the Waldorf-Astoria. At the opening evening session Dr. Harold L. Foss, of Danville, Pa., will be installed as president for the year 1953.

Annual Meeting of Western Institute on Epilepsy.—The Western Institute on Epilepsy will hold its fourth annual meeting in Los Angeles on Oct. 24 and 25, 1952. Previous Institutes have been of great interest to neurologists, psychiatrists, internists, general practitioners, social workers, psychologists, and, in fact, anyone interested in the problems of epilepsy. The Fourth Western Institute will be particularly designed for the general practitioner and pediatrician, as well as for public health officials and school personnel interested in the epileptic child and his school and home adjustments. For further information write Dr. Jean P. Davis, College of Medicine, University of Utah, 168 Westminster Ave., Salt Lake City, or Mrs. F. S. Markham, 1100 South Bay Front, Balboa Island, Calif.

Course in Postgraduate Gastroenterology.—The National Gastroenterological Association has announced that its Fourth Annual Course in Postgraduate Gastroenterology will be given at the Hotel Statler, New York, on Oct. 23, 24, and 25, 1952. The course will again be under the direction and co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, who will serve as surgical co-ordinator, and Dr. I. Snapper, Director of Medical Education of the Mount Sinai Hospital, New York, who will serve as medical co-ordinator. Subjects discussed will include diseases of the mouth, diseases of the esophagus, diseases of the stomach, diseases of the pancreas, psychosomatic aspects of gastrointestinal diseases, diseases of the liver and gall bladder, diseases of the pancreas and spleen, and diseases of the colon and rectum. Further information may be secured from the National Gastroenterological Association, Department GSJ, 1819 Broadway, New York 23.

National Gastroenterological Association Award Contest for 1952.—The National Gastroenterological Association has announced its Annual Cash Prize Award Contest for 1952. One hundred dollars and a Certificate of Merit will be given for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be selected by a board of impartial judges, and the award is to be made at the Annual Convention Banquet of the National Gastroenterological Association in October, 1952.

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The Association reserves the exclusive right of publishing the winning contribution, and those receiving Certificates of Merit, in its official publication, *The Review of Gastroenterology.*

All entries for the 1952 prize should be limited to 5,000 words, typewritten in English, prepared in manuscript form, and submitted in five copies accompanied with an entry letter and must be received not later than Sept. 1, 1952. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23.

Books

Renal Function: Transactions of the Second Conference, Oct. 19-20, 1950, New York. Edited by Stanley E. Bradley. Price, $3. Pp. 178, with charts and tables. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This record of the Second Conference on Renal Function emphasizes the influence of hormonal factors, specifically the secretions of the anterior pituitary, posterior pituitary, and adrenal cortex. There are excellent brief presentations of the general problems in the light of their own experimental work by R. Gaunt, H. G. Van Dyke, H. L. White, E. H. Burnett, F. Binkley, and J. A. Luetscher Jr.

Their discussions are supplemented by the informal question-and-answer and comment periods which distinguish these transactions from other scientific reports. They give the reader the feeling of personal participation in the symposium under the guidance and constructive criticism of recognized authorities.

While the material is presented on the level of the specialized investigator, any alert physician or senior medical student should be stimulated by the keen analysis of the physiological mechanisms regulating diuresis and by the ingenious applications of conclusions from experimental data to therapeutic problems in such human diseases as Addison's disease, the nephrotic syndrome, diabetes insipidus, and cirrhosis of the liver.

The Medical Clinics of North America. Chicago Number. Symposium on Recent Advances in Cardiovascular Diseases. Clinics on Other Subjects. By various authors. Price, $2.50. Pp. 1-301, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, January, 1952.

Twenty-five authors contributed 20 articles to this issue of *The Medical Clinics of North America.* Fifteen of the articles are grouped together in the form of a Symposium on Recent Advances in Cardiovascular Diseases. Such timely topics as the role of low-cholesterol diets in the prevention and treatment of atherosclerosis and a discussion on the congenital cardiovascular anomalies which are benefited by surgical intervention are comprehensively reviewed in easily readable outline form.

Of additional interest are an up-to-date review of some of the more important features in the clinical use of corticotropin (ACTH) and cortisone (by Dr. Edwin N. Irons) and an article dealing with practical problems in the use of antibiotics by Dr. H. F. Dowling and Dr. M. H. Lepper.

The Clinical Use of Fluid and Electrolyte. By John H. Bland, M.D. Price, $6.50. Pp. 259, with 75 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

This volume includes chapters on the basic physiology of body fluids and electrolytes; on the varieties of water and salt depletion, and on electrolyte and fluid disturbances in heart failure, postoperative states, renal disease, diabetes mellitus, adrenal cortical insufficiency, and various types of trauma. There are special chapters on potassium metabolism and on fluid balances in pediatrics and geriatrics. The text is profusely illustrated with "Gamblegrams."

Considering the scope of the discussion, the author has, in general, satisfied his aim "to provide a practical, usable guide to the recognition and treatment of the various fluid and electrolyte abnormalities that may arise in medical and surgical patients." It is to be all the more regretted, therefore, that the format is so unpalatable, with pages of long unbroken lines of monotonous type.

In the profusion of diagrams a number of errors have crept in which can be corrected later. There are also a few serious errors in interpretation; for example, the author speaks of the prevention of severe acidosis in heart failure with renal disease as effected by a loss of less

chloride than sodium and a decrease in the serum bicarbonate. He also describes cardiac edema fluid as hypertonic and speaks of the need of water by the kidneys to excrete the excess salt retained.

There is an excellent discussion on mercurial diuresis and the factors in refractoriness to mercurials. However, it would seem wiser to obtain serum electrolyte determinations than to wait for tetany and other clinical signs as the indication of hypochloremic metabolic alkalosis. One must disagree with him on the reliability of the urinary specific gravity, chloride, or pH estimations in attempting to make a chemical diagnosis.

It may be just as well that formulas for calculating electrolyte deficits are not given in the chapters on medical conditions, but are reserved for the one on surgical situations, since the latter are more likely to represent a true external depletion of electrolyte rather than dilution by retention of water.

The discussion on electrolyte changes in nephrosis is below the standard of the rest of the material. The author does not mention corticotropin (ACTH), cortisone, or human serum albumin in the treatment of nephrotic edema, nor does he allude to interesting material on diuretic experiments or the influence of antidiuretic and adrenal cortical hormones on tubular reabsorption of water and sodium in nephrosis. It is remarkable that in a special chapter on physiologic effects of corticotropin and cortisone, nothing is said regarding practical applications of this knowledge.

The preceding criticisms, however, point to relatively minor defects in comparison with the genuine value of this monograph, which is not only highly informative but very clearly written.

Fluid Balance: A Clinical Manual. By Carl A. Moyer, M.D. Price, $3.75. Pp. 191. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This book is of pocket manual size and is divided into 12 chapters of easily readable material pertaining to all phases of fluid balance, from the history of early studies and the physiology of water metabolism to the pathologic physiology, clinical signs and symptoms, and treatment of fluid imbalance. Particular attention is paid to the fluid and electrolyte problems in the post-operative patient, with the author pointing out some of the commoner pitfalls that may be encountered.

The book contains many informative charts, and each chapter is followed by a complete bibliography.

Liver Injury: Transactions of the Ninth Conference, April 27-28, 1950, New York. Edited by F. W. Hoffbauer. Price, $3. Pp. 232, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This publication of the 1950 Macy Conference on Liver Injury lives up to the high standard set in previous years. Of particular interest are the discussions on hepatic lymphatics, vascular physiology, and experimental dietary cirrhosis. It is virtually essential reading for all interested in disease of the liver.

Rx for Medical Writing: A Useful Guide to Principles and Practice of Effective Scientific Writing and Illustration. By Edwin P. Jordan, M.D., and Willard C. Shepard. Price, $2.50. Pp. 112, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadlephia 5, 1952.

The purpose of this volume is to aid the authors of medical papers in the proper presentation of a scientific paper and in avoidance of the many pitfalls that they may encounter in writing the paper and getting it accepted for publication.

The book covers preliminary steps, such as choice of subject, preparation of notes, outlining, and evaluation of the audience, and stresses the considerable importance of a first draft followed by at least three revisions to assure readability. Detailed recommendations on these phases of writing the paper are presented.

The book also contains comments and recommendations on the handling of special problems, such as the making of indices, the presentation and use of illustrations, and the proper use of statistics as employed in medical literature.

Seven appendices which cover abbreviations in medical manuscripts, proofreaders' marks, tables of atomic weights, drug dosages, temperature conversions, and statistical probability scales are included.

Cold Injury: Transactions of the First Conference, June 4-5, 1951, New York. Edited by M. Irene Ferrer, with many contributors. Price, $3.25. Pp. 248, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1952.

This conference was sponsored by the Josiah Macy, Jr., Foundation in the realization that the subject of cold injury overlaps a number of different disciplines in the general area of medicine. The topics discussed covered "Animal Studies," by Harris B. Shumacker Jr. and Jefferson M. Crismon; "Homeokinesis," by Steven M. Horvath; "Hypothermia," by John H. Talbott, with an additional report of experimental work in England by Otto G. Edholm. The conference concluded with a report on studies of "Acclimatization," by Robert Kark. These discussions are stimulating and will be of interest to many physicians.

Problems of Consciousness: Transactions of the Second Conference, March 19-20, 1951, New York. Edited by Harold A. Abramson, with many contributors. Price, $3.25. Pp. 178. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

These transactions of the Second Conference on Problems of Consciousness are presented in the same fashion as are those in other fields covered by the Macy conferences. The discussions are interesting and should be of value not only to psychiatrists but to clinicians, psychologists, and students of medicine as well. Many problems in the field are indicated by the discussions.

Connective Tissues: Transactions of the Second Conference, May 24-25, 1951, New York. Edited by Charles Ragan, with many contributors. Price, $3.50. Pp. 190, with 80 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1952.

The transactions of the second Macy Conference on Connective Tissue, like the previous transactions, are extremly interesting and important, especially with existing interest in corticotropin (ACTH) and cortisone and the present realization that connective tissue and related tissue and substances are not to be regarded as inactive material. These transactions present some of the ideas and studies of greatest interest today. This important book is highly recommended to those working in the field, as well as to others concerned with clinical and experimental medicine in general.

Peptic Ulcer: Clinical Aspects, Diagnosis, Management. Edited by David J. Sandweiss. Published under the auspices of the American Gastroenterological Association. Price, $15. Pp. 790, with 164 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

This book was planned and sponsored by the American Gastroenterological Association. It is a good example of how well a difficult subject can be handled by a group of experts such as these, whose special qualifications are so intimately known by the American Gastroenterological Association.

The book is of good paper with large readable print. Charts and photographs are simple and clear. The text is divided into eight sections with a number of chapters in each section. Nearly every chapter has a helpful summary and is well documented with selected references.

The first section (eight chapters) is an excellent discussion of the anatomy and physiology of the upper part of the gastrointestinal tract. This is followed by the section (ten chapters) on pathogenesis and etiology of peptic ulcer. Most of the small amount of criticism of this book that can be made centers on this section. The chapter on the general adaptation syndrome seems much too long and the material could perhaps have been absorbed in other chapters, as could the material on allergic factors. The section (eight chapters) on diagnosis and differential diagnosis is excellent, as would be expected with authors such as Bockus, Palmer, and Wilbur. The fourth section (thirteen chapters) on medical treatment is comprehensive and useful. Surgical treatment, its indications and results, is the concern of Section Five (eleven chapters), and it is covered well and with fairness. The presentation on peptic ulcer of the young

and the aged in Section Six (two chapters) should be examined by all internists. Ulcerations other than gastroduodenal are discussed in the next section (six chapters), and the final, eighth, section (six chapters) deals with the complications of gastroduodenal ulcer. All these chapters are well done, and particularly the chapter on electrolyte disturbances will bear careful reading.

This is not a book for the undergraduate medical student. It will and can be helpful to any physician but will be of most use to those internists with interest in gastroenterology. It is an excellent book, and the American Gastroenterological Association deserves congratulations.

Internal Medicine: Its Therapy and Practice. Edited by John H. Musser, M.D., with 80 contributors. Fifth edition. Edited by Michael G. Wohl, M.D. Price, $15. Pp. 1563, with 236 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1951.

With few exceptions, one looks in vain for any residue of Musser in the new Musser-Wohl "Internal Medicine"; most of the sections have been rewritten by new authors, but it may be said that Dr. Wohl has edited an excellent book in his own right.

Are more textbooks of medicine needed? That is a real question and one which the reviewer merely raises but does not attempt to answer. Certain it is that one man can no longer cover the whole field effectively, and to the present work 80 authors have contributed. It remains, then, for one editor to pit his team against the other teams; there will obviously be variations in the caliber of different contributors. The present Musser-Wohl edition seems to the reviewer a highly creditable performance. In many parts it is stronger than other popular texts; in some it is weaker. That could not be avoided. In all the current books, one wonders whether space allocated to rarities would not be better used for longer discussions of the diseases commonly encountered. For example, acute primary diaphragmitis receives a whole column; Aleppo boil (cutaneous leishmaniasis) gets three columns—all this contributes to the excessive physical weight of the volume. A good feature is the illustrations, which are well selected and adequately reproduced. The Musser-Wohl text can fairly take its place with the other popular American texts.

Liver Injury: Transactions of the Tenth Conference, May 21-22, 1951, New York. Edited by F. W. Hoffbauer, with many contributors. Price, $3.75. Pp. 320, with 42 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This book contains the transactions of the Tenth Conference on Liver Injury conducted by the Macy Foundation. It is concerned largely with aspects of lipid metabolism, a subject now on the crest of interest in metabolism in the medical field. Even though this subject may enter the trough again, those interested in liver function and disease, as well as in lipid metabolism, will find the discussions to be of interest. The circulation of the liver and the influence of ischemia on liver function are among the other topics discussed.

Anesthesia in General Practice. Third edition. By Stuart C. Cullen, M.D., Head of Division of Anesthesiology, State University of Iowa Hospital; Professor of Surgery (Anesthesiology), State University of Iowa College of Medicine. Price, $4.50. Pp. 292, with 36 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1951.

This is the third edition of a book whose excellence as a basic text in anesthesiology needs no elaboration. Originally projected from a series of lectures for senior medical students, it has developed into a useful book for all those interested in fundamentals; the emphasis throughout is upon basic principles rather than upon actual techniques. It is an unusually readable book with a set of illustrations and charts that are not easily overlooked or forgotten.

The third edition is similar to the previous editions in the section on depressant drugs. This chapter is perhaps one of the most useful in the book. The important drugs are discussed in regard to their use in both preoperative and postoperative medication. An invaluable part is the detailed treatment of effects from overdosage of depressant drugs.

The chapters on the airway and the various anesthetic agents continue as before to be excellent. The entire book is unreservedly recommended for all interested in anesthesiology.

Year Book of Medicine, 1951. Edited by P. B. Beeson and others. Price, $5. Pp. 696, with 149 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1951.

As in years past, the 1951 "Year Book of Medicine" contains the articles considered important by the various editors in the fields of infection; the chest; blood and blood-forming organs; heart, blood vessels, and kidney, and the digestive system. The five editors are eminently well qualified for their task of selecting significant contributions, and the short editorial comments are useful in evaluations by the average internist. Even voracious readers cannot cover the current literature of the whole field of internal medicine. For those who wish to keep reasonably well informed on special phases other than those of their own particular interest, this yearly volume is invaluable.

The "Year Book" quiz, prepared to arouse the interest of potential readers, includes such questions as the following, all answered in the summarized papers of this issue:

"What is perhaps the most promising agent now being studied as a cancer antagonist?

"Which is it, arteriolar dilatation or spasm, that produces intermittent claudication?

"Lobar pneumonia mortality rate was 20 to 40 per cent twenty years ago. What is it today?

"What stomach activity accounts for the alkaline tide in urine after meals?

"Oliguria and azotemia during rapid diuresis may give rise to what erroneous impression?"

The reviewer is fully aware of the flood of periodicals containing abstracts of all present medical literature, most of which he finds of no value. However, he unhesitatingly recommends the 1951 "Year Book of Medicine" because of the commendable way in which the selection of material and the editing have been done.

The Calculation of Industrial Disabilities of the Extremities. By Carl O. Rice, M.D., Ph.D. Price, $10.50. Pp. 284, with 204 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This monograph is designed to furnish a scale for calculation of disabilities of the extremities based on residual range of motion in the joints of the extremities. It is divided into six chapters; the first four deal with historical and anatomic considerations, relative values, and fundamental principles of calculating disabilities. The last two chapters deal with specific disabilities of the upper and lower extremities. The entire basis for computing disability ratings, as proposed in this monograph, is the residual function in the extremity as measured by joint motion of the various component parts.

The illustrations in this monograph are excellent. The tables are easily read and function well as a quick source for reference. The only criticism of the method described in this monograph, and not of the monograph itself, concerns the author's failure to consider such functional limitations as might occur from pain and deformity of the part with relatively normal persistent motion in the joints. The author takes cognizance of this factor in his statement that ". . . it is realized that some disabilities defy measurements. To that extent the judgment of the surgeon must necessarily be relied upon." It is unfortunate that the author has not seen fit to include a specific method of evaluating industrial disabilities of the spine and trunk.

Clinical Pediatric Urology. By Dr. Meredith Campbell, M.D., Professor of Urology, The Post-Graduate Medical School of New York University; Visiting Urologist, Bellevue and University Hospitals, New York. With a Section on Nephritis and Allied Diseases in Infancy and Childhood by Elvira Goettsch, M.D., Associate Professor of Pediatrics, University of Southern California School of Medicine; Assistant Medical Director of the Children's Hospital Society of Los Angeles, and John D. Lyttle, M.D., Late Professor of Pediatrics, University of Southern California School of Medicine; Medical Director of the Children' Memorial Hospital Society of Los Angeles. Price, $18. Pp. 1113, with 543 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

This book is dedicated to the countless thousands of urologically handicapped children, and rightfully so. Only the father of present-day urology, Dr. Meredith Campbell, could present such a masterful work. The fact that this edition is in one volume makes it a handy reference book for the library of the general practitioner, pediatrician, urologist, abdominal surgeon, hospital resident, or intern.

The preface explains clearly the reasons for the progress of urology of infants and children. In each chapter the author's vast amount of experience and the mass of material he has been able to study are ably presented. Observations of other workers are freely cited. An extensive bibliography based on the author's studies of the world's literature pertaining to urology in infants and children is alphabetically arranged at the end of each chapter.

Every phase of urinary tract disease is covered systematically, including etiology, pathology, symptoms, diagnosis, and treatment. Definitive treatment is stressed in some conditions. The chapter on embryology and anomalies of the urogenital tract is well illustrated. The schema depicting the anomalies, colloid corrosive preparations, pyelographic studies, photographs of specimens, photomicrographs, and models are well synchronized and grouped to depict each case presented.

Understanding of the embryology of the genitourinary tract is essential to visualization and recognition of many pathological conditions of the involved organs, e. g., undescended testes, ectopic kidneys or ureters, hydrospadias, horseshoe kidney, and anomalous renal vessels producing hydronephrosis, to name but a few. These conditions are clearly and simply explained under their appropriate headings or divisions. The chapter on "Methods of Examination and Diagnosis" enumerates clearly the commonest causes of each symptom and sign. Some simple procedures employed by the author in examining patients should be helpful to any examiner.

The section on nephritis and allied diseases concludes the book. The authors of this section, with their vast amount of experience, are well qualified to write on these subjects. They admit that no satisfactory classification of Bright's disease can be formulated until more is known of the etiology and pathogenesis of the various forms of the disease. But provisional differentiation of the reversible from the irreversible forms of the disease must be made early in order to estimate prognosis for the parent.

This chapter covers the medical side of kidney disease, bringing forth the primary and secondary pathology of the kidney, together with associated disseminated pathology, such as renal rickets and renal dwarfism.

Table 25, a classification of the commoner types of Bright's disease in children, followed by a clear-cut discussion of each type of the disease, is very illuminating. The paragraphs on laboratory findings, clinical features and findings, diagnosis, differential diagnosis, prognosis, and treatment are well coordinated and instructive. The newer therapeutic agents, as corticotropin (ACTH) and cortisone, are discussed. Such a chapter is necessary to any well-rounded book on children's urology.

Modern Electrocardiography. Volume I. By Eugene Lepeschkin, M.D. Foreword by Frank N. Wilson, M.D. Price, $12. Pp. 598, with charts. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

This is an excellent book written by one of the foremost authorities in the field of electrocardiography, an opinion well expressed in Dr. F. N. Wilson's foreword. The author has written an excellent book in German, which, because of the language, is not widely known or employed in this country.

This book, Volume I, represents a consideration of the problems of electrocardiography other than disturbances in cardiac mechanisms; the latter will be presented in Volume II. Among the subjects discussed are electrocardiographs, artifacts, laws employed in electrocardiography, basic problems of electrocardiography, the electrocardiograms of various animals, physiologic factors that influence the electrocardiogram, influence of physical factors, pharmacologic factors including vitamins and hormones, conduction defects, infarction, hypertrophy, coronary insufficiency, myocarditis, and allergic states.

When it is realized that this volume contains only 600 pages, it becomes evident that the author has done extremely well in presenting comprehensively the data obtained from almost 10,000 references included in the bibliography. Because of the extensive nature of the bibliography, it is not surprising that errors relative to it are found. It is unfortunate that the author did not evaluate the material obtained from the literature more critically in an attempt to assist the newcomer in differentiating the good work from the poor. Instead he presents the material on electrocardiography found in the literature with the idea that some data of value are

present in almost all papers. An extremely valuable aspect of the book is the review of the entire European literature, made possible by the fortunate fact that the author reads all European languages.

Because Dr. Lepeschkin is directly involved in electrocardiographic research and is trained clinically, his interpretation and presentation of data are of value to everyone interested in electrocardiography, including the medical student, investigator, and practicing physician. There is no doubt that the average physician employing electrocardiography in his practice will have considerable difficulty appreciating the details of the book. This is surely not the fault of the author or of the book, because the material is presented well, but rather is due to the fact that few physicians who employ electrocardiography in the practice of medicine understand its principles.

Volume I is welcomed, and Volume II is awaited with interest. This is not just another book in the field of electrocardiography but a definitely superior one. It should meet with much success.

1951 Year Book of Drug Therapy. Edited by Harry Beckman, M.D. Price, $5. Pp. 502, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

As usual, Dr. Beckman has reviewed an enormous mass of medical literature on treatment and has made useful selections in all the various fields of drug therapy. Probably no one with primary interest in a particular medical specialty would agree that all the most significant contributions in that area had been adequately covered. However, the book, as usual, will be a great timesaver for those seeking a quick guide to recent advances in therapy. Those familiar with Dr. Beckman's fairness and competence in evaluation of new drugs might wish for more editorial comment. The 1951 edition of this useful series will be received eagerly by its old friends and will be found up to the high standards of its predecessors.

Textbook of Clinical Neurology. Third edition. By Johannes M. Nielsen. Price, $10. Pp. 709, with 212 illustrations. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1951.

The internist or general practitioner confronted with problems relating to the nervous system will find this book a real source of help. To make it a text for this purpose was evidently the object of the author. Everything in the book relates directly to clinical syndromes encountered in disorders of the brain and spinal cord.

There has been extensive revision of the second edition, the new chapter on intracranial angiography and newer developments in the management of cerebral thrombosis and embolism being among the important changes. The author is to be congratulated on a thoroughly adequate coverage of modern knowledge of the complex group of conditions with which he is dealing. The book is profusely illustrated and printed on good paper with large, clear type. It should prove popular with all clinicians.

Significance of the Body Fluids in Clinical Medicine. By L. H. Newburgh. Price, $2. Pp. 76, with 16 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

This compact monograph reviews in simple, lucid terms the basic physiology and methods of calculation necessary for the understanding of body fluids, including sections on composition, adjustment of pH, and respiratory and renal regulation. The second part of the work is concerned with the clinical significance of the various abnormalities of pattern most commonly encountered.

The clinician will find this a ready means of refreshing and correlating his knowledge on a complex subject that is of daily importance. The book is written in a logical and sequential manner, presenting the normal and pathologic mechanisms without becoming unnecessarily involved in theoretical chemistry. The book is not, nor was it intended to be, a handbook of fluid therapy, but it is a review of an important phase of practical physiology well presented.

Surgery and the Endocrine System. By James D. Hardy, M.D. Price, $5. Pp. 153, with 42 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

Although the material presented in this little book is perfectly sound, there really seems very little reason for a special treatise on this subject. Actually the first third of the volume is on general matters, such as nutrition, electrolytes, and early ambulation. The special sections are somewhat sketchy; the tumors of the pituitary, for example, are dealt with in two pages. However, surgeons may find useful hints here or may quickly orient themselves on some point.

Cancer Cytology of the Uterus: Introducing a Concept of Cervical Cell Pathology. By J. Ernest Ayre. Price, $14.50. Pp. 407, with 362 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1951.

The author of this book has been influential in the present trend of early diagnoses in carcinoma of the cervix, diagnoses prior to the stage of invasion or prior to the appearance of a grossly evident lesion. His "cervical scrape method" of obtaining cytology smears from the cervix has undoubtedly increased the accuracy of this diagnostic procedure.

The present book is a beautiful example of the bookmaker's art. Three hundred sixty-two illustrations are included. A few of these are in color.

The subject of the book, as the title implies, is highly technical. It would be of interest only to those who interpret or wish to learn how to interpret cytology smears. The reviewer, however, could not recommend the book unreservedly even for such persons. It must be granted that much of the volume is admirable. On the other hand, there are places where it is more than difficult to differentiate between facts and the author's hypotheses or beliefs. This is particularly evident in his large section on "nearo-carcinoma," a term he has coined and uses almost synonymously for his self-explanatory but questionable concept of "precancer cell complex."

Disorders of the Heart and Circulation. Edited by Robert L. Levy, M.D. Price, $12. Pp. 944, with illustrations. Thos. Nelson & Sons, 385 Madison Ave., New York 17 [medical book-publishing business purchased by Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2], 1949-1951.

This recent addition to the literature on cardiovascular diseases is a compilation of 34 monographs which originally appeared in "Nelson's Loose-Leaf Medicine."

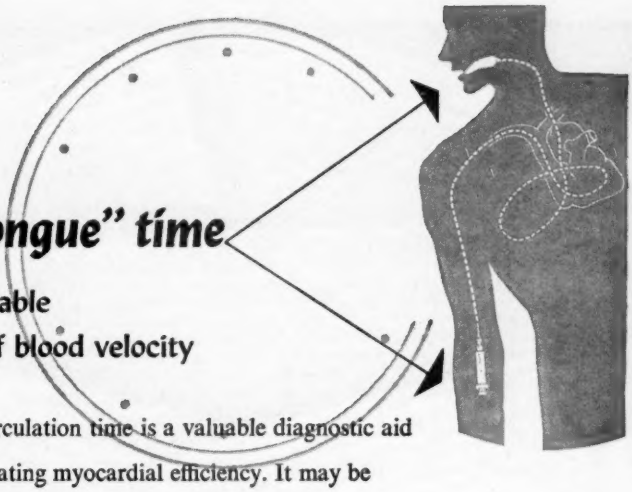
The 41 distinguished authors have done a thorough and well-integrated job in presenting their subject matter to the reader. One may refer to the volume with confidence that any clinically important topic concerning the heart or blood vessels will be dealt with in a scholarly manner.

However, the book cannot be considered a ready clinical guide for the busy practitioner. It is not easy reading in many places, and its details on the history of heart disease, etiology, pathology, and physiology definitely make it a reference tome.

The chapters concerning physiology of congenital heart disease, electrocardiography, rheumatic heart disease, and the carotid sinus syndrome are especially interesting.

The editor in his treatment of coronary insufficiency does not, to the reviewer's mind, state the case for and against exercise-tolerance tests quite as objectively as someone less closely identified with the anoxia test might have done. The complete omission of the technique of the exercise test will no doubt cause some readers to judge the chapter as inadequate.

On the whole, however, the text can be recommended as an excellent reference source to those interested in detailed study of the cardiovascular system.



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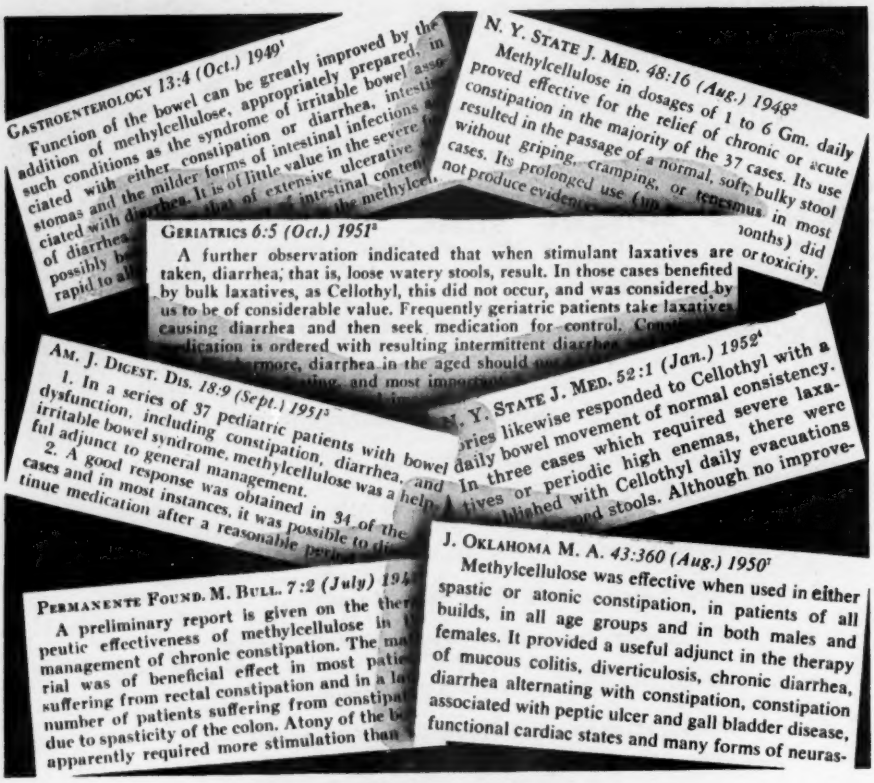
GASTROENTEROLOGY 13:4 (Oct.) 1949[1]
Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared, in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea, intestinal stomas and the milder forms of intestinal infections associated with diarrhea. It is of little value in the severe forms of diarrhea, that of extensive ulcerative colitis, possibly because of intestinal content... rapid to allow the methylcel...
N. Y. STATE J. MED. 48:16 (Aug.) 1948[2]
Methylcellulose in dosages of 1 to 6 Gm. daily proved effective for the relief of chronic or acute constipation in the majority of the 37 cases. Its use resulted in the passage of a normal, soft, bulky stool without griping, cramping, or tenesmus in most cases. Its prolonged use (up ... months) did not produce evidence ... or toxicity.
GERIATRICS 6:5 (Oct.) 1951[3]
A further observation indicated that when stimulant laxatives are taken, diarrhea, that is, loose watery stools, result. In those cases benefited by bulk laxatives, as Cellothyl, this did not occur, and was considered by us to be of considerable value. Frequently geriatric patients take laxatives causing diarrhea and then seek medication for control. Constipation is ordered with resulting intermittent diarrhea. ... Furthermore, diarrhea in the aged should not be ... ating, and most important ...
AM. J. DIGEST. DIS. 18:9 (Sept.) 1951[5]
1. In a series of 37 pediatric patients with bowel dysfunction, including constipation, diarrhea, and irritable bowel syndrome, methylcellulose was a helpful adjunct to general management.
2. A good response was obtained in 34 of the cases and in most instances, it was possible to discontinue medication after a reasonable period ...
N. Y. STATE J. MED. 52:1 (Jan.) 1952[4]
...ories likewise responded to Cellothyl with a daily bowel movement of normal consistency. In three cases which required severe laxatives or periodic high enemas, there were established with Cellothyl daily evacuations of formed stools. Although no improve...
PERMANENTE FOUND. M. BULL. 7:2 (July) 194...
A preliminary report is given on the therapeutic effectiveness of methylcellulose in the management of chronic constipation. The material was of beneficial effect in most patients suffering from rectal constipation and in a large number of patients suffering from constipation due to spasticity of the colon. Atony of the bowel apparently required more stimulation than ...
J. OKLAHOMA M. A. 43:360 (Aug.) 1950[7]
Methylcellulose was effective when used in either spastic or atonic constipation, in patients of all builds, in all age groups and in both males and females. It provided a useful adjunct in the therapy of mucous colitis, diverticulosis, chronic diarrhea, diarrhea alternating with constipation, constipation associated with peptic ulcer and gall bladder disease, functional cardiac states and many forms of neuras-

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Bibliography: 1. Bargen, J. A. 2. Schweig, K. 3. Wechsler, L.; Kessler, L. A., and Goldsmith, M. F. 4. Keeler, K. C., and Rusk, H. A. 5. Seidmon, E. E. P. 6. Newey, J. A., and Goetzl, F. R. 7. Musick, V. H.

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1. Hutcheson, J. M.: Management of Cardiac Failure. *Virginia Med. Monthly*, 74:458, Oct., 1947.
2. Noth, P. H.: Pick's Disease: A Record of Eight Years' Treatment with Salyrgan, Ammonium Nitrate, and Abdominal Paracentesis. *Proc. Staff Meet. Mayo Clin.*, 12:513, Aug. 18, 1937.

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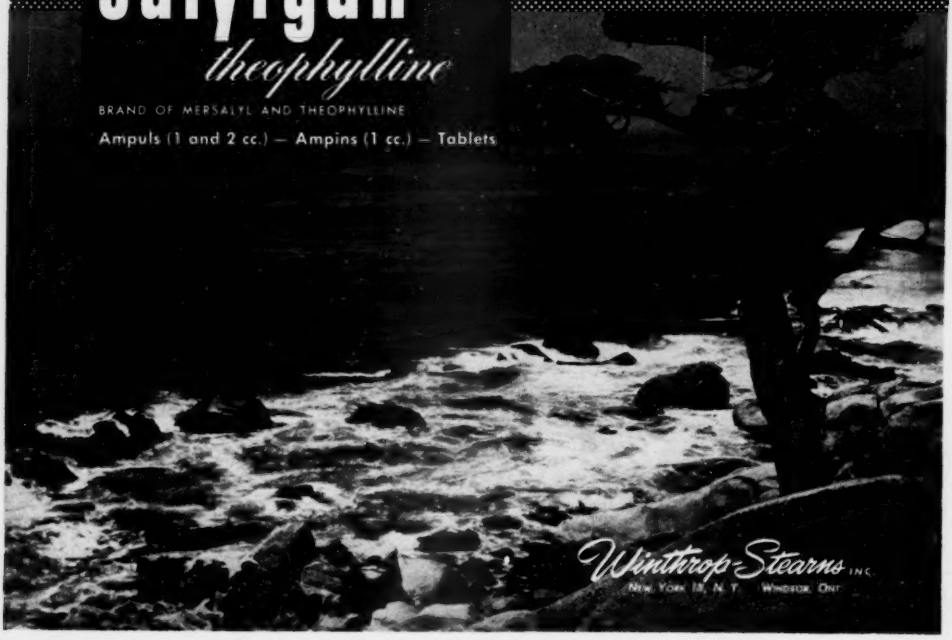

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